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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :

C12N 15/31, 15/62, C07K 14/315, A61K
39/09

A2

(11) International Publication Number:

WO 00/39299

(43) International Publication Date:

6 July 2000 (06.07.00)

(21) International Application Number: PCT/CA99/01218

(22) International Filing Date: 20 December 1999 (20.12.99)

(30) Priority Data:

60/113,800

23 December 1998 (23.12.98) US

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG,
BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE,
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE,
LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT,
BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished
upon receipt of that report.

(54) Title: NOVEL STREPTOCOCCUS ANTIGENS

BVH11-2 SP64	BVH11 SP63	BVH11 JNR.7/87	BVH11-2 JNR.7/87	BVH11 WU2	BVH11-2 WU2	BVH11 A66	BVH11-2 A66	BVH11 P4241	BVH11-2 P4241	BVH11 Rx-1	BVH11-2 Rx-1	BVH11 SP64
I81% S86%	I88% S90%	I88% S91%	I82% S87%	I80% S85%	I80% S85%	I80% S85%	I80% S85%	I80% S85%	I80% S85%	I88% S91%	I81% S85%	BVH11 SP64
	I87% S90%	I87% S90%	I98% S98%	I95% S96%	I96% S97%	I95% S96%	I96% S97%	I95% S96%	I96% S97%	I87% S91%	I94% S95%	BVH11-2 SP64
		I96% S96%	I88% S91%	I88% S91%	I87% S90%	I88% S91%	I87% S90%	I88% S91%	I87% S90%	I97% S97%	I89% S91%	BVH11 SP63
			I87% S90%	I86% S91%	I87% S91%	I86% S91%	I87% S91%	I86% S91%	I87% S91%	I96% S96%	I88% S90%	BVH11 JNR.7/87
				I96% S97%	I97% S97%	I96% S97%	I97% S97%	I96% S97%	I97% S97%	I87% S90%	I94% S93%	BVH11-2 JNR.7/87
					I98% S98%	I92% S94%	I98% S98%	I99% S99%	I98% S98%	I87% S91%	I92% S94%	BVH11 WU2
						I98% S98%	I99% S99%	I98% S98%	I99% S99%	I86% S90%	I93% S93%	BVH11-2 WU2
							I99% S99%	I98% S98%	I99% S99%	I87% S91%	I92% S94%	BVH11 A66
								I99% S99%	I99% S99%	I86% S90%	I93% S93%	BVH11-2 A66
									I99% S99%	I87% S91%	I92% S94%	BVH11 P4241
										I86% S90%	I93% S93%	BVH11-2 P4241
											I91% S92%	BVH11 Rx-1

(57) Abstract

Streptococcus proteins and polynucleotides encoding them are disclosed. Said proteins are antigenic and therefore useful vaccine components for the prophylaxis or therapy of streptococcus infection in animals. Also disclosed are recombinant methods of producing the protein antigens as well as diagnostic assays for detecting streptococcus bacterial infection.

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NOVEL STREPTOCOCCUS ANTIGENS

FIELD OF THE INVENTION

- 5 The present invention is related to antigens, more particularly protein antigens of streptococcus pneumoniae pathogen which are useful as vaccine components for therapy and/or prophylaxis.

10 BACKGROUND OF THE INVENTION

- S. pneumoniae is an important agent of disease in man especially among infants, the elderly and immunocompromised persons. It is a bacterium frequently isolated from
- 15 patients with invasive diseases such as bacteraemia/septicaemia, pneumonia, meningitis with high morbidity and mortality throughout the world. Even with appropriate antibiotic therapy, pneumococcal infections still result in many deaths. Although the advent of
- 20 antimicrobial drugs has reduced the overall mortality from pneumococcal disease, the presence of resistant pneumococcal organisms has become a major problem in the world today. Effective pneumococcal vaccines could have a major impact on the morbidity and mortality associated with S. pneumoniae
- 25 disease. Such vaccines would also potentially be useful to prevent otitis media in infants and young children.

- Efforts to develop a pneumococcal vaccine have generally concentrated on generating immune responses to the
- 30 pneumococcal capsular polysaccharide. More than 80 pneumococcal capsular serotypes have been identified on the basis of antigenic differences. The currently available pneumococcal vaccine, comprising 23 capsular polysaccharides

that most frequently caused disease, has significant shortcomings related primarily to the poor immunogenicity of some capsular polysaccharides, the diversity of the serotypes and the differences in the distribution of serotypes over time, geographic areas and age groups. In particular, the failure of existing vaccines and capsular conjugate vaccines currently in development to protect young children against all serotypes spurs evaluation of other S. pneumoniae components. Although immunogenicity of capsular polysaccharides can be improved, serotype specificity will still represent a major limitation of polysaccharide-based vaccines. The use of an antigenically conserved immunogenic pneumococcal protein antigen, either by itself or in combination with additional components, offers the possibility of a protein-based pneumococcal vaccine.

PCT Publication number WO98/18930 published May 7 1998 entitled "*Streptococcus Pneumoniae* antigens and vaccines" describes certain polypeptides which are claimed to be antigenic. However, no biological activity of these polypeptides is reported.

Therefore there remains an unmet need for *Streptococcus* antigens that may be used as vaccine components for the prophylaxis and/or therapy of *Streptococcus* infection.

SUMMARY OF THE INVENTION

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55

to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

5 In other aspects, there are provided vectors comprising polynucleotides of the invention operably linked to an expression control region, as well as host cells transfected with said vectors and methods of producing polypeptides comprising culturing said host cells under conditions suitable for expression.

10

In yet another aspect, there are provided novel polypeptides encoded by polynucleotides of the invention.

15 **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 is the DNA sequence of BVH-3 gene; SEQ ID NO: 1.

20 Figure 2 is the amino acid sequence of BVH-3 protein; SEQ ID NO: 2.

Figure 3 is the DNA sequence of BVH-11 gene; SEQ ID NO: 3.

25 Figure 4 is the amino acid sequence of BVH-11 protein; SEQ ID NO: 4.

Figure 5 is the DNA sequence of BVH-28 gene; SEQ ID NO: 5.

30 Figure 6 is the amino acid sequence of BVH-28 protein; SEQ ID NO: 6.

Figure 7 is the DNA sequence of BVH-3A gene which corresponds to the 5' terminal end of BVH-3; SEQ ID NO: 7.

Figure 8 is the amino acid sequence of BVH-3A protein; **SEQ ID NO: 8.**

Figure 9 is the DNA sequence of BVH-3B gene which
5 corresponds to the 3' terminal end of BVH-3; **SEQ ID NO: 9.**

Figure 10 is the amino acid sequence of BVH-3B protein; **SEQ ID NO: 10.**

10 Figure 11 depicts the comparison of the predicted amino acid sequences of the BVH-3 open reading frames from WU2, RX1, JNR.7/87, SP64, P4241 and A66 S. pneumoniae strains by using the program Clustal W from MacVector sequence
15 analysis software (version 6.5). Underneath the alignment, there is a consensus line where * and . characters indicate identical and similar amino acid residues, respectively.

Figure 12 depicts the comparison of the predicted amino
20 acid sequences of the BVH-11 open reading frames from WU2, Rx1, JNR.7/87, SP64, P4241, A66 and SP63 S. pneumoniae strains by using the program Clustal W from MacVector sequence analysis software (version 6.5). Underneath the alignment, there is a consensus line where * and .
25 characters indicate identical and similar amino acid residues, respectively.

Figure 13 depicts the comparison of the predicted amino acid sequences of the BVH-11 proteins from various S.
30 pneumoniae strains. The degrees of identity (I) and similarity (S) were determined by using the program Clustal W from MacVector sequence analysis software (version 6.5).

Figure 14 is a DNA sequence containing the complete BVH-3
35 gene (open reading frame "ORF" at nucleotides 1777 to 4896); **SEQ ID NO: 11.**

Figure 15 is a DNA sequence containing the complete BVH-11 gene (ORF at nucleotides 45 to 2567); **SEQ ID NO: 12.**

- 5 Figure 16 is a DNA sequence containing the complete BVH-11-2 gene (ORF at nucleotides 114 to 2630); **SEQ ID NO: 13.**

Figure 17 is the amino acid sequence of BVH-11-2 protein; **SEQ ID NO: 14.**

10

Figure 18 is the DNA sequence of SP63 BVH-3 gene; **SEQ ID NO: 15.**

- 15 Figure 19 is the amino acid sequence of SP63 BVH-3 protein; **SEQ ID NO: 16.**

Figure 20 is the amino acid sequence of BVH-3M protein; **SEQ ID NO: 55.**

- 20 Figure 21 is the amino acid sequence of BVH-3AD protein; **SEQ ID NO: 56.**

Figure 22 is the amino acid sequence of L-BVH-3-AD protein; **SEQ ID NO: 57.**

25

Figure 23 is the amino acid sequence of NEW12 protein; **SEQ ID NO: 58.**

- 30 Figure 24 is the amino acid sequence of BVH-3C protein; **SEQ ID NO: 59.**

Figure 25 is the amino acid sequence of BVH-11M protein; **SEQ ID NO: 60.**

- 35 Figure 26 is the amino acid sequence of BVH-11A protein; **SEQ ID NO: 61.**

Figure 27 is the amino acid sequence of BVH-11B (also called New13) protein; **SEQ ID NO: 62.**

- 5 Figure 28 is the amino acid sequence of BVH-11C protein;
SEQ ID NO: 63.

Figure 29 is the amino acid sequence of NEW1 protein; **SEQ ID NO: 64.**

10

Figure 30 is the amino acid sequence of NEW2 protein; **SEQ ID NO: 65.**

- 15 Figure 31 is the amino acid sequence of NEW3 protein; **SEQ ID NO: 66.**

Figure 32 is the amino acid sequence of NEW4 protein; **SEQ ID NO: 67.**

- 20 Figure 33 is the amino acid sequence of NEW5 protein; **SEQ ID NO: 68.**

Figure 34 is the amino acid sequence of NEW6 protein; **SEQ ID NO: 69.**

25

Figure 35 is the amino acid sequence of NEW7 protein; **SEQ ID NO: 70.**

- 30 Figure 36 is the amino acid sequence of NEW8 protein; **SEQ ID NO: 71.**

Figure 37 is the amino acid sequence of NEW9 protein; **SEQ ID NO: 72.**

- 35 Figure 38 is the amino acid sequence of BVH-11-2M protein;
SEQ ID NO: 73.

Figure 39 is the amino acid sequence of NEW10 protein; SEQ ID NO: 74.

- 5 Figure 40 is the amino acid sequence of NEW11 protein; SEQ ID NO: 75.

Figure 41 is the DNA sequence of NEW12 gene; SEQ ID NO: 76.

- 10 Figure 42 is the amino acid sequence of NEW14 protein; SEQ ID NO: 77.

Figure 43 is the amino acid sequence of NEW15 protein; SEQ ID NO: 78.

15

Figure 44 is the amino acid sequence of NEW16 protein; SEQ ID NO: 79.

- 20 Figure 45 is the DNA sequence of GBS BVH-71 gene; SEQ ID NO: 80.

Figure 46 is the amino acid sequence of GBS BVH-71 protein; SEQ ID NO: 81.

- 25 Figure 47 is the DNA sequence of GAS BVH-71 gene; SEQ ID NO: 82.

Figure 48 is the amino acid sequence of GAS BVH-71 protein; SEQ ID NO: 83.

30

DETAILED DESCRIPTION OF THE INVENTION

- 35 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55

to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

5 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 95% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

10 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOS: 2, 4, 8, 10, 14, 16, 55 to 15 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at 20 least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOS: 2, 4, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

25 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOS: 2, 4, 8, 10, 14, 16, 55 to 75, 77 to 79 or fragments, analogs or derivatives thereof.

30 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOS: 2, 8, 10, 16, 55, 56, 57, 35 58, 59, 64, 65, 66, 78 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 8, 10, 16, 55, 56, 57, 59, 64, 65, 66, 78 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 4, 14, 58, 60, 61, 62, 63, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 79 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 4, 14, 60, 61, 62, 63, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 79 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 10, 14, 16, 55 to 75, 77 to 79 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence chosen from SEQ ID NOs: 10, 55 to 75, 77, 78, 79 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an

isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence chosen from **SEQ ID NOS: 55 to 75, 77, 78, 79** or fragments, analogs or derivatives thereof.

5

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOS: 2, 4, 6, 8, 10** or
10 fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at
15 least 70% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOS: 2, 4, 10, 14, 16** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an
20 isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from **SEQ ID NOS: 2, 4, 14, 16** or fragments, analogs or derivatives thereof.

25 According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 2** or fragments, analogs or derivatives thereof.

30

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising
35 sequence **SEQ ID NO: 4** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 10** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 14** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 16** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 58** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 60** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 62** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 64** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 67** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 68** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 69** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 72** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence **SEQ ID NO: 74** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising sequence SEQ ID NO: 77 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NOS: 2, 4, 6, 8, 10 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NOS: 2, 4, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NOS: 2, 4, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NOS: 2, 4, 8, 10, 14, 16, 55 to 75, 77 to 79 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NOS: 2, 4, 10, 14, 16, 55 to 75, 77 to 79 or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOS: 2, 4, 10, 14, 16** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 2** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 4** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 10** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 14** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 16** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from **SEQ ID NOS: 10, 55 to 75, 77, 78, 79** or fragments, analogs or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NO: 10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof.

5

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NO: 10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof.

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According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NO: 10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof.

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According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence chosen from SEQ ID NO: 10, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof.

20

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence SEQ ID NO: 58 or fragments, analogs or derivatives thereof.

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According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence SEQ ID NO: 62 or fragments, analogs or derivatives thereof.

30

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence SEQ ID NO: 64 or fragments, analogs or derivatives thereof.

35

According to one aspect, the present invention relates to

polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 67** or fragments, analogs or derivatives thereof.

- 5 According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 68** or fragments, analogs or derivatives thereof.
- 10 According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 74** or fragments, analogs or derivatives thereof.
- 15 According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising sequence **SEQ ID NO: 77** or fragments, analogs or derivatives thereof.
- 20 In a further embodiment, the present invention also relates to chimeric polypeptides which comprise one or more polypeptides or fragments, analogs or derivatives thereof as described in the present application.
- 25 In a further embodiment, the present invention also relates to chimeric polypeptides which comprise one or more polypeptides or fragments, analogs or derivatives thereof as defined in the figures of the present application.
- 30 In a further embodiment, the present application also relates to chimeric polypeptides which comprise two or more polypeptides chosen from **SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83** or fragments, analogs or derivatives thereof ;provided that the polypeptides or
35 fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.

In a further embodiment, the chimeric polypeptide will comprise two or more polypeptides chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or
5 fragments, analogs or derivatives thereof; provided that the polypeptides or fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.

In a further embodiment, the chimeric polypeptide will
10 comprise two or more polypeptides chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof; provided that the polypeptides or fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.

15 In a further embodiment, the chimeric polypeptide will comprise two or more polypeptides chosen from SEQ ID NOS :10, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof; provided that the polypeptides or
20 fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.

In a further embodiment, the chimeric polypeptide will comprise between 2 and 5 polypeptides.
25

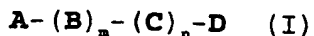
In a further embodiment, the chimeric polypeptide will comprise between 2 and 4 polypeptides.

In a further embodiment, the chimeric polypeptide will
30 comprise between 2 and 3 polypeptides.

In a further embodiment, the chimeric polypeptide will comprise 2 polypeptides.

35

In a further embodiment, there is provided a chimeric polypeptide of formula (I):



5 Wherein;

 m is 0 or 1,

 n is 0 or 1,

 A is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to
10 75, 77 to 79, 81, 83 or fragments, analogs or derivatives
 thereof;

 B is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to
 75, 77 to 79, 81, 83 or fragments, analogs or derivatives
 thereof;

 C is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to
15 75, 77 to 79, 81, 83 or fragments, analogs or derivatives
 thereof; and

 D is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to
 75, 77 to 79, 81, 83 or fragments, analogs or derivatives
 thereof.

20

 In a further embodiment,

 A is chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68,
 69, 72, 74, 77 or fragments, analogs or derivatives
 thereof;

25 B is chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68,
 69, 72, 74, 77, or fragments, analogs or derivatives
 thereof;

 C is chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68,
 69, 72, 74, 77 or fragments, analogs or derivatives
30 thereof; and

 D is chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68,
 69, 72, 74, 77 or fragments, analogs or derivatives
 thereof.

35 In a further embodiment,

- A is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof;
B is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 74, 77, or fragments, analogs or derivatives thereof;
5 C is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof; and
D is chosen from SEQ ID NOs :10, 58, 60, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof.
- 10 In one embodiment, chimeric polypeptides of the present invention comprise those wherein the following embodiments are present, either independently or in combination.
- In a further embodiment, A is SEQ ID NOs :10, 58, 62, 64,
15 67, 68, 74, 77 or fragments, analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :10 or fragments, analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :58 or fragments,
20 analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :62 or fragments, analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :64 or fragments, analogs or derivatives thereof.
- 25 In a further embodiment, A is SEQ ID NO :67 or fragments, analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :68 or fragments, analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :74 or fragments,
30 analogs or derivatives thereof.
- In a further embodiment, A is SEQ ID NO :77 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NOS :10, 58, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof.

5 In a further embodiment, B is SEQ ID NO :10 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NO :58 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NO :64 or fragments, analogs or derivatives thereof.

10 In a further embodiment, B is SEQ ID NO :64 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NO :67 or fragments, analogs or derivatives thereof.

15 In a further embodiment, B is SEQ ID NO :68 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NO :74 or fragments, analogs or derivatives thereof.

In a further embodiment, B is SEQ ID NO : 77 or fragments, analogs or derivatives thereof.

20 In a further embodiment, C is SEQ ID NOS :10, 58, 62, 64, 67, 68, 74, 77 or fragments, analogs or derivatives thereof.

25 In a further embodiment, C is SEQ ID NO :10 or fragments, analogs or derivatives thereof.

In a further embodiment, C is SEQ ID NO :58 or fragments, analogs or derivatives thereof.

In a further embodiment, C is SEQ ID NO : 62 or fragments, analogs or derivatives thereof.

30 In a further embodiment, C is SEQ ID NO :64 or fragments, analogs or derivatives thereof.

In a further embodiment, C is SEQ ID NO : 67 or fragments, analogs or derivatives thereof.

In a further embodiment, C is SEQ ID NO : 68 or fragments,

analog or derivatives thereof.

In a further embodiment, C is SEQ ID NO : 74 or fragments, analog or derivatives thereof.

In a further embodiment, C is SEQ ID NO : 77 or fragments,
5 analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :10, 58, 62, 64, 67, 68, 74, 77 or fragments, analog or derivatives thereof.

10 In a further embodiment, D is SEQ ID NO :10 or fragments, analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :58 or fragments, analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :62 or fragments,
15 analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :64 or fragments, analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :67 or fragments, analog or derivatives thereof.

20 In a further embodiment, D is SEQ ID NO :68 or fragments, analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :74 or fragments, analog or derivatives thereof.

In a further embodiment, D is SEQ ID NO :77 or fragments,
25 analog or derivatives thereof.

In a further embodiment, m is 0.

In a further embodiment, n is 0.

30

In a further embodiment, m and n are 0.

In a further embodiment, m and n are 0, A is SEQ ID NO:64 or fragments, analog or derivatives thereof, B is SEQ ID

NO:62 or fragments, analogs or derivatives thereof.

In a further embodiment, m and n are 0, A is SEQ ID NO:62 or fragments, analogs or derivatives thereof, B is SEQ ID NO:64 or fragments, analogs or derivatives thereof.

5

In accordance with the present invention, all nucleotides encoding polypeptides and chimeric polypeptides are within the scope of the present invention.

- 10 In a further embodiment, the polypeptides or chimeric polypeptides in accordance with the present invention are antigenic.

- In a further embodiment, the polypeptides or chimeric
15 polypeptides in accordance with the present invention can elicit an immune response in an individual.

- In a further embodiment, the present invention also relates to polypeptides which are able to raise antibodies having
20 binding specificity to the polypeptides or chimeric polypeptides of the present invention as defined above.

- An antibody that "has binding specificity" is an antibody that recognizes and binds the selected polypeptide but
25 which does not substantially recognize and bind other molecules in a sample, e.g., a biological sample, which naturally includes the selected peptide. Specific binding can be measured using an ELISA assay in which the selected polypeptide is used as an antigen.

30

- Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent
35 applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In

case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

5

As used herein, "fragments", "derivatives" or "analogs" of the polypeptides of the invention include those polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably conserved) and which may be natural or unnatural. In one embodiment, derivatives and analogs of polypeptides of the invention will have about 70% identity with those sequences illustrated in the figures or fragments thereof. That is, 70% of the residues are the same. In a further embodiment, polypeptides will have greater than 75% homology. In a further embodiment, polypeptides will have greater than 80% homology. In a further embodiment, polypeptides will have greater than 85% homology. In a further embodiment, polypeptides will have greater than 90% homology. In a further embodiment, polypeptides will have greater than 95% homology. In a further embodiment, polypeptides will have greater than 99% homology. In a further embodiment, derivatives and analogs of polypeptides of the invention will have fewer than about 20 amino acid residue substitutions, modifications or deletions and more preferably less than 10. Preferred substitutions are those known in the art as conserved i.e. the substituted residues share physical or chemical properties such as hydrophobicity, size, charge or functional groups.

30

In accordance with the present invention, polypeptides of the invention include both polypeptides and chimeric polypeptides.

35

Also included are polypeptides which have fused thereto

other compounds which alter the polypeptides biological or pharmacological properties i.e. polyethylene glycol (PEG) to increase half-life; leader or secretory amino acid sequences for ease of purification; prepro- and pro-
5 sequences; and (poly)saccharides.

Furthermore, in those situations where amino acid regions are found to be polymorphic, it may be desirable to vary one or more particular amino acids to more effectively
10 mimic the different epitopes of the different streptococcus strains.

Moreover, the polypeptides of the present invention can be modified by terminal $-NH_2$ acylation (eg. by acetylation, or
15 thioglycolic acid amidation, terminal carboxy amidation, e.g. with ammonia or methylamine) to provide stability, increased hydrophobicity for linking or binding to a support or other molecule.

Also contemplated are hetero and homo polypeptide multimers of the polypeptide fragments, analogues and derivatives. These polymeric forms include, for example, one or more polypeptides that have been cross-linked with cross-linkers such as avidin/biotin, gluteraldehyde or dimethyl-
20 superimide. Such polymeric forms also include polypeptides containing two or more tandem or inverted contiguous sequences, produced from multicistronic mRNAs generated by recombinant DNA technology. Preferably, a fragment, analog or derivative of a
30 polypeptide of the invention will comprise at least one antigenic region i.e. at least one epitope.

In order to achieve the formation of antigenic polymers (i.e. synthetic multimers), polypeptides may be utilized
35 having bishaloacetyl groups, nitroarylhalides, or the like, where the reagents being specific for thio groups.

Therefore, the link between two mercapto groups of the different peptides may be a single bond or may be composed of a linking group of at least two, typically at least four, and not more than 16, but usually not more than about 14 carbon atoms.

In a particular embodiment, polypeptide fragments, analogs and derivatives of the invention do not contain a methionine (Met) starting residue. Preferably, polypeptides will not incorporate a leader or secretory sequence (signal sequence). The signal portion of a polypeptide of the invention may be determined according to established molecular biological techniques. In general, the polypeptide of interest may be isolated from a streptococcus culture and subsequently sequenced to determine the initial residue of the mature protein and therefore the sequence of the mature polypeptide.

According to another aspect, there are provided vaccine compositions comprising one or more streptococcus polypeptides of the invention in admixture with a pharmaceutically acceptable carrier diluent or adjuvant. Suitable adjuvants include oils i.e. Freund's complete or incomplete adjuvant; salts i.e. $\text{AlK}(\text{SO}_4)_3$, $\text{AlNa}(\text{SO}_4)_2$, $\text{AlNH}_4(\text{SO}_4)_2$, silica, kaolin, carbon polynucleotides i.e. poly IC and poly AU. Preferred adjuvants include QuilA and Alhydrogel. Vaccines of the invention may be administered parenterally by injection, rapid infusion, nasopharyngeal absorption, dermoabsorption, or bucal or oral. Pharmaceutically acceptable carriers also include tetanus toxoid.

Vaccine compositions of the invention are used for the treatment or prophylaxis of streptococcus infection and/or diseases and symptoms mediated by streptococcus infection as described in P.R. Murray (Ed, in chief), E.J. Baron, M.A.

Pfaller, F.C. Tenover and R.H. Tenover. Manual of Clinical Microbiology, ASM Press, Washington, D.C. sixth edition, 1995, 1482p which are herein incorporated by reference. In one embodiment, vaccine compositions of the present invention are used for the treatment or prophylaxis of meningitis, otitis media, bacteremia or pneumonia. In one embodiment, vaccine compositions of the invention are used for the treatment or prophylaxis of streptococcus infection and/or diseases and symptoms mediated by streptococcus infection, in particular S.pneumoniae, group A streptococcus (pyogenes), group B streptococcus (GBS or agalactiae), dysgalactiae, uberis, nocardia as well as Staphylococcus aureus. In a further embodiment, the streptococcus infection is S.pneumoniae.

In a particular embodiment, vaccines are administered to those individuals at risk of streptococcus infection such as infants, elderly and immunocompromised individuals.

As used in the present application, the term " individuals" include mammals. In a further embodiment, the mammal is human.

Vaccine compositions are preferably in unit dosage form of about 0.001 to 100 µg/kg (antigen/body weight) and more preferably 0.01 to 10 µg/kg and most preferably 0.1 to 1 µg/kg 1 to 3 times with an interval of about 1 to 6 week intervals between immunizations.

According to another aspect, there are provided polynucleotides encoding polypeptides characterized by the amino acid sequence chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

- In one embodiment, polynucleotides are those illustrated in
SEQ ID Nos: 1, 3, 5, 7, 9, 11, 12, 13, 15, 76, 80, 82
which may include the open reading frames (ORF), encoding
polypeptides of the invention. It will be appreciated that
5 the polynucleotide sequences illustrated in the figures may
be altered with degenerate codons yet still encode the
polypeptides of the invention. Accordingly the present
invention further provides polynucleotides which hybridize
to the polynucleotide sequences herein above described (or
10 the complement sequences thereof) having 50% identity
between sequences. In one embodiment, at least 70% identity
between sequences. In one embodiment, at least 75% identity
between sequences. In one embodiment, at least 80% identity
between sequences. In one embodiment, at least 85% identity
15 between sequences. In one embodiment, at least 90% identity
between sequences. In a further embodiment, polynucleotides
are hybridizable under stringent conditions i.e. having at
least 95% identity. In a further embodiment, more than 97%
identity.
- 20 In a further embodiment, polynucleotides are those
illustrated in **SEQ ID NOs : 1, 3, 7, 9, 11, 12, 13, 15, 76,
80, 82** encoding polypeptides of the invention.
- 25 In a further embodiment, polynucleotides are those
illustrated in **SEQ ID NOs : 1, 3, 9, 11, 12, 13, 15, 76,
80, 82** which may include the open reading frames (ORF),
encoding polypeptides of the invention.
- 30 In a further embodiment, polynucleotides are those
illustrated in **SEQ ID NOs : 1, 3, 9, 11, 12, 13, 15, 76**
which may include the open reading frames (ORF), encoding
polypeptides of the invention.
- 35 In a further embodiment, polynucleotides are those

illustrated in **SEQ ID NOS : 1, 3, 7, 9, 11, 12, 13, 15, 76** which may include the open reading frames (ORF), encoding polypeptides of the invention.

- 5 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NOS : 1, 7, 9, 11, 15, 76** which may include the open reading frames (ORF), encoding polypeptides of the invention.
- 10 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NOS : 1, 9, 11, 15, 76** which may include the open reading frames (ORF), encoding polypeptides of the invention.
- 15 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NOS : 1, 7, 9, 11** which may include the open reading frames (ORF), encoding polypeptides of the invention.
- 20 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO : 1**, encoding polypeptides of the invention.
- In a further embodiment, polynucleotides are those
25 illustrated in **SEQ ID NO : 7**, encoding polypeptides of the invention.
- In a further embodiment, polynucleotides are those
illustrated in **SEQ ID NO : 9**, encoding polypeptides of the
30 invention.
- In a further embodiment, polynucleotides are those
illustrated in **SEQ ID NO : 11**, encoding polypeptides of the
invention.

35

In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :15**, encoding polypeptides of the invention.

- 5 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NOS : 3, 12, 13, 76**, encoding polypeptides of the invention.

- 10 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :3**, encoding polypeptides of the invention.

- 15 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :12**, encoding polypeptides of the invention.

- 20 In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :13**, encoding polypeptides of the invention.

- In a further embodiment, polynucleotides are those illustrated in **SEQ ID NO :76**, encoding polypeptides of the invention.

- 25 As will be readily appreciated by one skilled in the art, polynucleotides include both DNA and RNA.

- 30 The present invention also includes polynucleotides complementary to the polynucleotides described in the present application.

- 35 In a further aspect, polynucleotides encoding polypeptides of the invention, or fragments, analogs or derivatives thereof, may be used in a DNA immunization method. That is, they can be incorporated into a vector which is

replicable and expressible upon injection thereby producing the antigenic polypeptide in vivo. For example polynucleotides may be incorporated into a plasmid vector under the control of the CMV promoter which is functional in eukaryotic cells. Preferably the vector is injected intramuscularly.

According to another aspect, there is provided a process for producing polypeptides of the invention by recombinant techniques by expressing a polynucleotide encoding said polypeptide in a host cell and recovering the expressed polypeptide product. Alternatively, the polypeptides can be produced according to established synthetic chemical techniques i.e. solution phase or solid phase synthesis of oligopeptides which are ligated to produce the full polypeptide (block ligation).

General methods for obtention and evaluation of polynucleotides and polypeptides are described in the following references: Sambrook et al, Molecular Cloning: A Laboratory Manual, 2nd ed, Cold Spring Harbor, N.Y., 1989; Current Protocols in Molecular Biology, Edited by Ausubel F.M. et al., John Wiley and Sons, Inc. New York; PCR Cloning Protocols, from Molecular Cloning to Genetic Engineering, Edited by White B.A., Humana Press, Totowa, New Jersey, 1997, 490 pages; Protein Purification, Principles and Practices, Scopes R.K., Springer-Verlag, New York, 3rd Edition, 1993, 380 pages; Current Protocols in Immunology, Edited by Coligan J.E. et al., John Wiley & Sons Inc., New York which are herein incorporated by reference.

For recombinant production, host cells are transfected with vectors which encode the polypeptide, and then cultured in a nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the genes.

Suitable vectors are those that are viable and replicable in the chosen host and include chromosomal, non-chromosomal and synthetic DNA sequences e.g. bacterial plasmids, phage DNA, baculovirus, yeast plasmids, vectors derived from combinations of plasmids and phage DNA. The polypeptide sequence may be incorporated in the vector at the appropriate site using restriction enzymes such that it is operably linked to an expression control region comprising a promoter, ribosome binding site (consensus region or Shine-Dalgarno sequence), and optionally an operator (control element). One can select individual components of the expression control region that are appropriate for a given host and vector according to established molecular biology principles (Sambrook et al, Molecular Cloning: A Laboratory Manual, 2nd ed, Cold Spring Harbor, N.Y., 1989; Current Protocols in Molecular Biology, Edited by Ausubel F.M. et al., John Wiley and Sons, Inc. New York incorporated herein by reference). Suitable promoters include but are not limited to LTR or SV40 promoter, E.coli lac, tac or trp promoters and the phage lambda P_t promoter. Vectors will preferably incorporate an origin of replication as well as selection markers i.e. ampicillin resistance gene. Suitable bacterial vectors include pET, pQE70, pQE60, pQE-9, pbs, pD10 phagescript, psiX174, pbluescript SK, pbsks, pNH8A, pNH16a, pNH18A, pNH46A, ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 and eukaryotic vectors pBlueBacIII, pWLNEO, pSV2CAT, pOG44, pXT1, pSG, pSVK3, pBPV, pMSG and pSVL. Host cells may be bacterial i.e. E.coli, Bacillus subtilis, Streptomyces; fungal i.e. Aspergillus niger, Aspergillus nidulins; yeast i.e. Saccharomyces or eukaryotic i.e. CHO, COS.

Upon expression of the polypeptide in culture, cells are typically harvested by centrifugation then disrupted by physical or chemical means (if the expressed polypeptide is not secreted into the media) and the resulting crude

extract retained to isolate the polypeptide of interest. Purification of the polypeptide from culture media or lysate may be achieved by established techniques depending on the properties of the polypeptide i.e. using ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxylapatite chromatography and lectin chromatography. Final purification may be achieved using HPLC.

10

The polypeptide may be expressed with or without a leader or secretion sequence. In the former case the leader may be removed using post-translational processing (see US 4,431,739; US 4,425,437; and US 4,338,397 incorporated herein by reference) or be chemically removed subsequent to purifying the expressed polypeptide.

According to a further aspect, the streptococcus polypeptides of the invention may be used in a diagnostic test for streptococcus infection, in particular S. pneumoniae infection. Several diagnostic methods are possible, for example detecting streptococcus organism in a biological sample, the following procedure may be followed:

- a) obtaining a biological sample from a patient;
- 25 b) incubating an antibody or fragment thereof reactive with a streptococcus polypeptide of the invention with the biological sample to form a mixture; and
- c) detecting specifically bound antibody or bound fragment in the mixture which indicates the presence
- 30 of streptococcus.

Alternatively, a method for the detection of antibody specific to a streptococcus antigen in a biological sample containing or suspected of containing said antibody may be performed as follows:

35

- a) obtaining a biological sample from a patient;

- b) incubating one or more streptococcus polypeptides of the invention or fragments thereof with the biological sample to form a mixture; and
- c) detecting specifically bound antigen or bound fragment in the mixture which indicates the presence of antibody specific to streptococcus.

One of skill in the art will recognize that this diagnostic test may take several forms, including an immunological test such as an enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay or a latex agglutination assay, essentially to determine whether antibodies specific for the protein are present in an organism.

- The DNA sequences encoding polypeptides of the invention may also be used to design DNA probes for use in detecting the presence of streptococcus in a biological sample suspected of containing such bacteria. The detection method of this invention comprises:
- a) obtaining the biological sample from a patient;
 - b) incubating one or more DNA probes having a DNA sequence encoding a polypeptide of the invention or fragments thereof with the biological sample to form a mixture; and
 - c) detecting specifically bound DNA probe in the mixture which indicates the presence of streptococcus bacteria.

The DNA probes of this invention may also be used for detecting circulating streptococcus i.e. S.pneumoniae nucleic acids in a sample, for example using a polymerase chain reaction, as a method of diagnosing streptococcus infections. The probe may be synthesized using conventional techniques and may be immobilized on a solid phase, or may be labelled with a detectable label. A preferred DNA probe for this application is an oligomer

having a sequence complementary to at least about 6 contiguous nucleotides of the streptococcus pneumoniae polypeptides of the invention.

- 5 Another diagnostic method for the detection of streptococcus in a patient comprises:
- a) labelling an antibody reactive with a polypeptide of the invention or fragment thereof with a detectable label;
 - 10 b) administering the labelled antibody or labelled fragment to the patient; and
 - c) detecting specifically bound labelled antibody or labelled fragment in the patient which indicates the presence of streptococcus.

15 A further aspect of the invention is the use of the streptococcus polypeptides of the invention as immunogens for the production of specific antibodies for the diagnosis and in particular the treatment of streptococcus infection.

20 Suitable antibodies may be determined using appropriate screening methods, for example by measuring the ability of a particular antibody to passively protect against streptococcus infection in a test model. One example of an animal model is the mouse model described in the examples

25 herein. The antibody may be a whole antibody or an antigen-binding fragment thereof and may belong to any immunoglobulin class. The antibody or fragment may be of animal origin, specifically of mammalian origin and more specifically of murine, rat or human origin. It may be a

30 natural antibody or a fragment thereof, or if desired, a recombinant antibody or antibody fragment. The term recombinant antibody or antibody fragment means antibody or antibody fragment which was produced using molecular biology techniques. The antibody or antibody fragments may

35 be polyclonal, or preferably monoclonal. It may be specific for a number of epitopes associated with the

streptococcus pneumoniae polypeptides but is preferably specific for one.

Without limiting its scope, the present invention also relates to new antigens designated BVH-3, BVH-11, BVH-11-2, BVH-28 and BVH-71. The present invention also relates to truncated polypeptides comprising fragments of the new antigens designated BVH-3, BVH-11, BVH-11-2, BVH-28 and BVH-71. The present invention also relates to chimeric polypeptides comprising fragments of the new antigens designated BVH-3, BVH-11, BVH-11-2, BVH-28 and BVH-71. The following is a reference table summarizing the relation between the antigens of the present invention:

Family	Nucleotide SEQ ID NO	Polypeptide SEQ ID NO
BVH-3		
BVH-3	1, 11	2
BVH-3A	7	8
BVH-3B	9	10
BVH-3 SP63	15	16
BVH-3M		55
BVH-3AD		56
L-BVH-3AD		57
New12	76	58
BVH-3C		59
New1		64
New2		65
New3		66
New15		78
BVH-11		
BVH-11	3, 12	4
BVH-11-2	13	14
BVH-11M		60
BVH-11A		61
BVH-11B also referred to as NEW13		62
BVH-11C		63
New4		67
New5		68

Family	Nucleotide SEQ ID NO	Polypeptide SEQ ID NO
New6		69
New7		70
New8		71
New9		72
BVH-11-2M		73
New10		74
New11		75
New12	76	58
New14		77
New16		79
BVH-28		
BVH-28	5	6
BVH-71		
GBS	80	81
GAS	82	83

EXAMPLE 1

- 5 This example illustrates the cloning of S. pneumoniae genes.

The coding region of S. pneumoniae gene BVH-3 (SEQ ID NO: 1) and the coding region of S. pneumoniae gene BVH-28 (SEQ ID NO: 5) were amplified by PCR (DNA Thermal Cycler GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from genomic DNA of serogroup 6 S. pneumoniae strain SP64 using the oligos that contained base extensions for the addition of restriction sites BglII (AGATCT) and XbaI (TCTAGA). PCR products were purified from agarose gel using a QIAquick gel extraction kit from QIAGEN (Chatsworth, CA), digested BglII-XbaI (Pharmacia Canada Inc, Baie d'Urfé, Canada), extracted with phenol : chloroform and precipitated with ethanol. The Superlinker vector pSL301 (Invitrogen, San Diego, CA) was digested with BglII and XbaI and purified from agarose gel using a QIAquick gel extraction kit from QIAGEN (Chatsworth, CA). The BglII-XbaI genomic DNA fragments were ligated to

the BglIII-XbaI pSL301 vector. The ligated products were transformed into *E. coli* strain DH5a [f80 lacZ DM15 endA1 recA1 hsdR17 (^rK^{-m}K⁺) supE44 thi-11⁻ gyrA96 relA1 D(lacZYA-argF)U169] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). Recombinant pSL301 plasmids (rpSL301) containing either BVH-3 or BVH-28 gene were purified using a QIAGEN kit (Chatsworth, CA) and DNA inserts were confirmed by nucleotide sequence analysis (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA). Recombinant rpSL301 (rpSL301) were digested with the restriction enzymes BglIII (AGATCT) and XhoI (CTCGAG). DNA fragments BglIII-XhoI were purified using the QIAquick gel extraction kit from QIAGEN (Chatsworth, CA). pET-32c(+) expression vector (Novagen, Madison, WI) containing the thioredoxin-His·Tag sequence was digested with BamHI (GGATCC) and XhoI and gel extracted using the QIAquick gel extraction kit from QIAGEN (Chatsworth, CA). The BglIII-XhoI DNA fragments were ligated to the BamHI-XhoI pET-32c(+) vector to create the coding sequence for thioredoxin-His·Tag-BVH-3 or thioredoxin-His·Tag-BVH-28 fusion protein. The ligated products were transformed into *E. coli* strain DH5a [f80 lacZ DM15 endA1 recA1 hsdR17 (^rK^{-m}K⁺) supE44 thi-11⁻ gyrA96 relA1 D(lacZYA-argF)U169] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). Recombinant pET-32c(+) plasmids were purified using a QIAGEN kit (Chatsworth, CA) and the nucleotide sequences at the fusion sites of thioredoxin-His·Tag and DNA insert were verified by DNA sequencing (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA).

EXAMPLE 2

This example illustrates the cloning of S. pneumoniae
5 protein genes in CMV plasmid pCMV-GH.

The DNA coding region of a S. pneumoniae protein was
inserted in phase downstream of a human growth hormone (hGH)
gene which was under the transcriptional control of the
10 cytomegalavirus (CMV) promotor in the plasmid vector pCMV-GH
(Tang et al., Nature, 1992, 356 :152). The CMV promotor is
non functional plasmid in E. coli cells but active upon
administration of the plasmid in eukaryotic cells. The
vector also incorporated the ampicillin resistance gene.

15 The coding region of BVH-3 gene (SEQ ID NO: 1) and BVH-28
gene (SEQ ID NO: 5) were obtained from rpSL301 (see example
1) using restriction enzymes BglII (AGATCT) and XbaI
(TCTAGA). The digested products were purified from agarose
20 gel using the QIAquick gel extraction kit from QIAGEN
(Chatsworth, CA). The pCMV-GH vector (Laboratory of Dr.
Stephen A. Johnston, Department of Biochemistry, The
University of Texas, Dallas, Texas) containing the human
growth hormone to create fusion proteins was digested with
25 BglII and XbaI and purified from agarose gel using the
QIAquick gel extraction kit from QIAGEN (Chatsworth, CA).
The BglII-XbaI DNA fragments were ligated to the BglII-XbaI
pCMV-GH vector to create the hGH-BVH-3 or hGH-BVH-28 fusion
protein under the control of the CMV promoter. The ligated
30 products were transformed into E. coli strain DH5a[f80 lacZ
DM15 endA1 recA1 hsdR17 (^rK⁻M⁺) supE44 thi-11⁻ gyrA96 relA1
D(lacZYA-argF)U169] (Gibco BRL, Gaithersburg, MD) according

to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). The recombinant pCMV plasmids were purified using a QIAgen kit (QIAgen, Chatsworth, CA).

5

The coding region of BVH-11 gene (SEQ ID NO: 3) was amplified by PCR (DNA Thermal Cyclor GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from genomic DNA of serogroup 6 S. pneumoniae strain SP64 using the oligos that contained
10 base extensions for the addition of restriction sites BglIII (AGATCT) and HindIII (AAGCTT). The PCR product was purified from agarose gel using a QIAquick gel extraction kit from QIAgen (Chatsworth, CA), digested with restriction enzymes (Pharmacia Canada Inc, Baie d'Urfe, Canada), extracted with
15 phenol : chloroform and precipitated with ethanol. The pCMV-GH vector (Laboratory of Dr. Stephen A. Johnston, Department of Biochemistry, The University of Texas, Dallas, Texas) was digested with BglIII and HindIII and purified from agarose gel using the QIAquick gel extraction kit from
20 QIAgen (Chatsworth, CA). The BglIII-HindIII DNA fragment was ligated to the BglIII-HindIII pCMV-GH vector to create the hGH-BVH-11 fusion protein under the control of the CMV promoter. The ligated products were transformed into E. coli strain DH5a[f80 lacZ DM15 endA1 recA1 hsdR17 (^rK⁻ K⁺) supE44
25 thi-11⁻ gyrA96 relA1 D(lacZYA-argF)U169] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). The recombinant pCMV plasmid was purified using a QIAgen kit (Chatsworth, CA) and the nucleotide sequence of
30 the DNA insert was verified by DNA sequencing.

EXAMPLE 3

This example illustrates the use of DNA to elicit an immune response to S. pneumoniae antigens.

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A group of 8 female BALB/c mice (Charles River, St-Constant, Québec, Canada) were immunized by intramuscular injection of 50 µl three times at two- or three-week intervals with 100 µg of recombinant pCMV-GH encoding the BVH-3, BVH-11 or the
10 BVH-28 gene in presence of 50 µg of granulocyte-macrophage colony-stimulating factor (GM-CSF)- expressing plasmid pCMV-GH-GM-CSF (Laboratory of Dr. Stephen A. Johnston, Department of Biochemistry, The University of Texas, Dallas, Texas).
As control, a group of mice were injected with 100 µg of
15 pCMV-GH in presence of 50 µg of pCMV-GH-GM-CSF. Blood samples were collected from the orbital prior to each immunization and seven days following the third injection and serum antibody responses were determined by ELISA using
thioredoxin-His-Tag-S. pneumoniae fusion protein as coating
20 antigen. DNA immunization with recombinant plasmid pCMV-GH encoding the BVH-3, BVH-11 or the BVH-28 S. pneumoniae protein induced antibody reactive against the respective recombinant protein. The reciprocal antibody titers, defined as the highest serum dilution at which the absorbance values
25 were 0.1 above the background values, were above 4×10^3 .

EXAMPLE 4

30 This example illustrates the production and purification of recombinant S. pneumoniae proteins.

The recombinant pET plasmids containing the BVH-3, BVH-11 or the BVH-28 gene corresponding to the SEQ ID NO: 1 , SEQ ID NO: 3 or the SEQ ID NO: 5 respectively were transformed by electroporation (Gene Pulser II apparatus, BIO-RAD Labs, Mississauga, Canada) into *E. coli* strain AD494 (DE3) (Dara⁻ leu7697 DlacX74 DphoA PvuII phoR DmalF3 F' [lac⁺(lacI^q) pro] trxB::Kan) (Novagen, Madison, WI). In this strain of *E. coli*, the T7 promotor controlling expression of the fusion protein is specifically recognized by the T7 RNA polymerase (present on the lDE3 prophage) whose gene is under the control of the lac promotor which is inducible by isopropyl-β-d-thio-galactopyranoside (IPTG). The transformant AD494(DE3)/rpET was grown at 37°C with agitation at 250 rpm in LB broth (peptone 10g/L, yeast extract 5g/L, NaCl 10g/L) containing 100μg of ampicillin (Sigma-Aldrich Canada Ltd., Oakville, Canada) per ml until the A₆₀₀ reached a value of 0.6. In order to induce the production of the thioredoxin-His·Tag-BVH-3, thioredoxin-His·Tag-BVH-11 or thioredoxin-His·Tag-BVH-28 fusion protein, the cells were incubated for 2 additional hours in the presence of IPTG at a final concentration of 1 mM. Induced cells from a 100 ml culture were pelleted by centrifugation and frozen at -70°C.

The purification of the fusion proteins from the soluble cytoplasmic fraction of IPTG-induced AD494(DE3)/rpET was done by affinity chromatography based on the properties of the His·Tag sequence (6 consecutive histidine residues) to bind to divalent cations (Ni²⁺) immobilized on the His·Bind metal chelation resin. Briefly, the pelleted cells obtained from a 100mL culture induced with IPTG were resuspended in

phosphate-buffered (PBS):500mM NaCl pH7.1, sonicated and spun at 20,000 X g for 20 min to remove debris. The supernatant was filtered (0.22µm pore size membrane) and deposited on a HiTrap® 1mL chelating pre-packed ready-to-use column (Pharmacia Biotech, Baie d'Urfé, Canada). The thioredoxin-His-Tag-S. pneumoniae fusion protein was eluted with 1M imidazole-500mM NaCl-PBS pH7.1. The removal of the salt and imidazole from the sample was done by dialysis against PBS at 4°C. The quantities of fusion protein obtained from the soluble fraction of E. coli was estimated by MicroBCA (Pierce, Rockford, Illinois).

EXAMPLE 5

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This example illustrates the protection of mice against fatal pneumococcal infection by immunization.

Groups of 8 female BALB/c mice (Charles River) were immunized subcutaneously three times at three-week intervals with either 25 µg of affinity purified thioredoxin-His-Tag-BVH-3 fusion protein in presence of 15 µg of QuilA adjuvant (Cedarlane Laboratories Ltd, Hornby, Canada) or, as control, with QuilA adjuvant alone in PBS. Blood samples were collected from the orbital sinus on day 1, 22 and 43 prior to each immunization and seven days (day 50) following the third injection. One week later the mice were challenged with approximately 10^6 CFU of the type 3 S. pneumoniae strain WU2. Samples of the S. pneumoniae challenge inoculum were plated on chocolate agar plates to determine the CFU and to verify the challenge dose. Deaths were recorded for

a period of 14 days and on day 14 post-challenge, the surviving mice were sacrificed and blood samples tested for the presence of S. pneumoniae organisms. The survival data are shown in table 1.

5

Prechallenge sera were analyzed for the presence of antibodies reactive with S. pneumoniae by standard immunoassays. Elisa and immunoblot analyses indicated that immunization with recombinant S. pneumoniae protein produced
10 in E. coli elicited antibodies reactive with both, recombinant and native pneumococcal protein.

Table 1. Protection mediated by recombinant BVH-3 protein

Immunogen	No. of mice alive : no. of mice dead 14 days post-challenge	Median day of death
BVH-3	8 : 0	>14
none	0 : 8	1

15

All mice immunized with BVH-3 recombinant protein survived to infection while none of the control mice given adjuvant alone survived. There was a significant difference in survival between the two groups of mice ($P < 0.0001$, log rank
20 test for nonparametric analysis of survival curves; $P = 0.0002$, Fisher's exact test). All hemocultures from surviving mice were negative at day 14 post-challenge.

25

EXAMPLE 6

This example describes the cloning of BVH-3 and BVH-11 genes from a variety of S. pneumoniae strains and the molecular conservation of these genes.

- 5 Molecular analysis of chromosomal DNA from various S. pneumoniae isolates with DNA probes spanning different regions of BVH-3 or BVH-11 revealed the presence of one BVH-3 gene copy and two BVH-11 gene copies. The two BVH-11 gene copies are not identical and the genes were
- 10 arbitrarily designated BVH-11 (SEQ ID NO:12; ORF at nucleotides 45 to 2567) and BVH-11-2 (SEQ ID NO:13; ORF at nucleotides 114 to 2630).

- The first amino acids of the BVH-3 and BVH-11 coding
- 15 regions have the characteristics of leader sequences also known as signal peptides. The consensus signal peptidase cleavage site L-X-X-C of lipoprotein modification/processing sites was present in the sequences. Mature BVH-3, BVH-11 and BVH-11-2 proteins from S. pneumoniae SP64 have 1019, 821 and 819 amino acids,
- 20 respectively. The regions of S. pneumoniae genes coding for mature BVH-3, termed BVH-3M, (nucleotides 1837 - 4896; SEQ. ID. NO: 11), BVH-11M (nucleotides 102-2567; SEQ. ID. NO: 12) and BVH-11-2M (nucleotides 171-2630; SEQ. ID. NO:
- 25 13), were amplified by PCR (DNA Thermal Cycler GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from genomic DNA of 6 or 7 S. pneumoniae strains. Serogroup 6 S. pneumoniae SP64 and serogroup 9 SP63 clinical isolates were provided by the laboratoire de la santé publique du Québec, Sainte-
- 30 Anne-de-Bellevue; serotype 4 strain JNR.7/87 was provided by Andrew Camilli, Tufts University School of Medicine, Boston; Rx1 strain, a nonencapsulated derivative of the type 2 strain D39 and the type 3 strains A66 and WU2 were provided by David E. Briles from University of Alabama,
- 35 Birmingham and the type 3 clinical isolate P4241 was provided by the centre de recherche en infectiologie du

centre hospitalier de l'université Laval, Sainte-Foy. The sets of oligonucleotide primers OCRR479-OCRR480; HAMJ160-OCRR488 and HAMJ160-HAMJ186, that contained base extensions for the addition of restriction sites were used for the amplification of BVH-3, BVH-11 and BVH-11-2 gene, respectively, with the exception of BVH-11 gene from SP64 strain which was amplified using the set of primers consisting of HAMJ487 and OCRR488. Primer sequences are listed below (Table 2). PCR products were purified from agarose gel using a QIAquick gel extraction kit from QIAgen (Chatsworth, CA) and digested BglIII-XbaI or BglIII-HindIII (Pharmacia Canada Inc, Baie d'Urfé, Canada). Digestions were cleaned using a QIAquick PCR purification kit from QIAgen (Chatsworth, CA). The PCR products were ligated to the BglIII-XbaI or BglIII-HindIII pSL301 vector. The ligated products were transformed into *E. coli* strain DH5 α [ϕ 80 *lacZ* Δ M15 *endA1* *recA1* *hsdR17* (^{*}K⁻K^{*}) *supE44* *thi-1* λ *gyrA96* *relA1* Δ (*lacZYA-argF*)U169] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). Recombinant pSL301 plasmids (rpSL301) containing BVH-3, BVH-11 or BVH11-2 were purified using a QIAgen kit (Chatsworth, CA) and DNA inserts were sequenced (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA). The figures 11 and 12 depict the consensus sequence established from the BVH-3, and BVH-11 deduced amino acid sequences, respectively. Comparison of BVH-3 protein sequences revealed 99 to 100% identity of sequences for all strains with the exception that BVH-3 from serogroup 9 SP63 strain (SEQ. ID. NO: 15 and SEQ. ID. NO: 16) misses a stretch of 177 amino acids corresponding to residues 244 to 420 on BVH-3'protein sequence of *S. pneumoniae* SP64. Analysis of sequences of additional serogroup 9 strains revealed BVH-3 molecule having the same deletion in 3 out of 4 strains

thus suggesting that the 3 strains are members of a S. pneumoniae serogroup 9 clone.

Comparison of 13 BVH-11 nucleotide sequences obtained from
5 7 S. pneumoniae strains, revealed that the nucleotide
sequences are very similar. Computer analysis (MacVector,
Clustal W 1.4) using multiple alignment of the predicted
BVH-11 protein sequences revealed that these sequences were
75% identical and 82 % homologous on a length of 834 amino
10 acids. Pairwise alignment revealed 80 to 100% identity
(Figure 13). The sequences showed great similarity in
overall organization. Variability in the primary sequence
of these proteins is almost restricted to the last 125
amino acids in the C-terminal portion of the proteins. This
15 region constitutes a domain. Close examination of this
domain revealed two groups of sequences. The first 9
sequences from the figure 13 belong to one group while the
last 4 sequences belong to another group. A 39% identity
value is obtained when the domain sequences of the 13
20 proteins are compared (MacVector, Clustal W 1.4). The
identity value increased to more than 92% when sequences
belonging to a same group are compared.

25 EXAMPLE 7

This example illustrates the homology of portions of BVH-3
and BVH-11 genes.

30 Molecular analysis with DNA probes derived from BVH-3 and
BVH-11 genes indicated that BVH-3 and BVH-11 were related.
In dot blot hybridization studies, DNA probe consisting of
either, BVH-3 or BVH-11, gene sequence hybridized to both,
BVH-3 and BVH-11 genes thus indicating that BVH-3 and BVH-
35 11 genes shared homologous sequences. Comparison of
sequences revealed that the ORFs and the proteins were 43

and 33% identical, respectively. Closer examination revealed that the region corresponding to amino acids 1 to 225 in BVH-3 and 1 to 228 in BVH-11 were 73 and 75% identical at the DNA and protein level, respectively. In contrast, the 3' regions corresponding to amino acids 226 to 1039 from BVH-3 and amino acids 229-840 from BVH-11 were only 34 and 22% identical at the DNA and protein level, respectively. Thus the 5' termini of BVH-3 and BVH-11 genes appear to contain highly conserved sequences while the remaining parts of the genes are highly divergent. These results suggest that BVH-3 and BVH-11 might share similar functions mediated by sequences present in the conserved region whereas BVH-3- and BVH-11-specific functions might be mediated by sequences in the divergent region.

EXAMPLE 8

This example describes the cloning of truncated BVH-3, BVH-11 and BVH-11-2 genes by polymerase chain reaction (PCR) and the expression of truncated BVH-3 and BVH-11 molecules.

Gene fragments were amplified by PCR using pairs of oligonucleotide engineered to amplify fragments spanning the BVH-3 (SEQ ID NO: 1 and SEQ ID NO: 11), BVH-11 (SEQ ID NO: 3 and SEQ ID NO: 12) or BVH-11-2 (SEQ ID NO: 13) gene from S. pneumoniae strain SP64. Each of the primers had a restriction endonuclease site at the 5' end, thereby allowing directional in-frame cloning of the amplified product into the digested plasmid vector (Tables 2 and 3). PCR-amplified products were digested with restriction endonucleases and ligated to either linearized plasmid pSL301 (see example 1), pCMV-GH (see example 2) or pET (Novagen, Madison, WI) expression vector digested likewise or digested with enzymes that produce compatible cohesive

ends. Recombinant pSL301 and recombinant pCMV-GH plasmids were digested with restriction enzymes for the in-frame cloning in pET expression vector. Clones were first stabilized in E. coli DH5 α before introduction into E. coli BL21(λ DE3) or AD494 (λ DE3) for expression of truncated BVH-3 or BVH-11 molecules. Each of the resultant plasmid constructs was confirmed by nucleotide sequence analysis. The recombinant proteins were expressed as N-terminal fusions with the thioredoxin and His-tag or as C-terminal fusions with an His-tag. The expressed recombinant proteins were purified from supernatant fractions obtained from centrifugation of sonicated IPTG-induced E. coli cultures using a His-Bind metal chelation resin (QIAgen, Chatsworth, CA). The gene products generated are listed in the table 3. The gene products corresponding to the N-terminal region including the signal sequence are designated as Lipidated-proteins or lipoproteins (L-proteins). The gene products corresponding to the N-terminal region lacking the signal sequence are identified as protein without signal sequence (w/o ss).

Table 2. List of PCR oligonucleotide primers

Primer	SEQ. ID.	Sequence 5' - 3'	Nucleotide position	Restriction sites
OCRR 479	17	cagtagatctgtgcctatgcactaac	SEQ ID 1:61-78	BglII
OCRR 480	18	gatctctagactactgctattccttacgctatg	SEQ ID 11:4909-4887	XbaI
OCRR 497	19	atcactcgagcattacctggataatcctgt	SEQ ID 1:1525-1506	XhoI
OCRR 498	20	ctgctaagcttatgaaagatttagat	SEQ ID 1:1534-1548	HindIII

OCRR 499	21	gatactcgagctgctattccttac	SEQ ID 11 :4906-4893	XhoI
HAMJ 172	22	gaatctcgagttaagctgctgctaattc	SEQ ID 1 : 675-661	XhoI
HAMJ 247	23	gacgctcgagcgctatgaaatcagataaattc	SEQ ID 1 :3117-3096	XhoI
HAMJ 248	24	gacgctcgagggcattacctggataatcctgttcattg	SEQ ID 1 :1527-1501	XhoI
HAMJ 249	25	cagtagatctcttcatttattgaaaagagg	SEQ ID 11 : 1749-1771	BglII
HAMJ 278	26	ttatttctccatattggacttgacagaagagcaaattaag	SEQ ID 1 :1414-1437	NdeI
HAMJ 279	27	cgccaagcttcgctatgaaatcagataaattc	SEQ ID 1 :3117-3096	HindIII
HAMJ 280	28	cgccaagctttccacaataataagtcgattgatt	SEQ ID 1 :2400-2377	HindIII
HAMJ 281	29	ttatttctccatattggaagtacattcttgaaaaagaa	SEQ ID 1 :2398-2421	NdeI
HAMJ 300	30	ttatttctccatattggtgcctatgcactaaaccagc	SEQ ID 1 :62-82	NdeI
HAMJ 313	31	ataagaatgcggccgctccacaataataagtcgattgatt	SEQ ID 1 :2400-2377	NotI
OCRR 487	32	cagtagatctgtgcttatgaactaggtttgc	SEQ ID 3 :58-79	BglII
OCRR 488	33	gatcaagcttgctgctacctttacttactctc	SEQ ID 12 :2577-2556	HindIII
HAMJ 171	34	ctgagatatccgttatcgttcaaac	SEQ ID 3 :1060-1075	EcoRV
HAMJ 251	35	ctgcaagcttttaagggaataatac	SEQ ID 3 :1059-1045	HindIII
HAMJ 264	36	cagtagatctgcagaagccctcctactg	SEQ ID 3 :682-700	BglII
HAMJ 282	37	tcgccaagcttcgttatcgttcaaacattggg	SEQ ID 3 :1060-1081	HindIII
HAMJ 283	38	ataagaatgcggccgcttactctcctttaataagccaat agtt	SEQ ID 3 :2520-2492	NdeI
HAMJ 284	39	catgccatggacattgatagctcttgaaacagc	SEQ ID 3 :856-880	NcoI
HAMJ 285	40	cgccaagcttcttactctcctttaataagccaatag	SEQ ID 3 :2520-2494	HindIII
HAMJ 286	41	cgacaagcttaacatggtcgctagcgttacc	SEQ ID 3 :2139-2119	HindIII
HAMJ 287	42	cataccatgggcctttatgaggcacctaag	SEQ ID 3 :2014-2034	NcoI
HAMJ 288	43	cgacaagcttaagtaaatcttcagcctctctcag	SEQ ID 3 :2376-2353	HindIII

HAMJ 289	44	gataccatggctagcgaccatgttcaaagaa	SEQ ID 3 :2125-2146	NcoI
HAMJ 290	45	cgccaagcttatcatccactaacttgactttatcac	SEQ ID 3 :1533-1508	HindIII
HAMJ 291	46	cataccatggatattcttgcttcttagctccg	SEQ ID 3 :1531-1554	NcoI
HAMJ 301	47	catgccatgggtgcttatgaactaggtttgc	SEQ ID 3 :59- 79	NcoI
HAMJ 302	48	cgccaagctttagcggttaccaaaaccattatc	SEQ ID 3 :2128-2107	HindIII
HAMJ 160	49	gtattagatctgttcctatgaactggctgacacca	SEQ ID 13 : 172-196	BglII
HAMJ 186	50	cgcctctagactactgtataggagccgg	SEQ ID 13: 2460-2443	XbaI
HAMJ 292	51	catgccatggaaaacatttcaagcctttacgtg	SEQ ID 11: 754-778	NcoI
HAMJ 293	52	cgacaagcttctgtataggagccggttgactttc	SEQ ID 11 : 2457-2434	HindIII
HAMJ 294	53	catgccatgggtcgtahaaataaggcagaccaag	SEQ ID 11 : 2038-2062	NcoI
HAMJ 297	54	catgccatggaagcctattggaatgggaag	SEQ ID 11 : 622-642	NcoI

Table 3. Lists of truncated BVH-3 and BVH-11 gene products generated from S. pneumoniae SP64

PCR-primer sets	Protein designation	Identification (encoded amino acids)	SEQ. ID.NO.	Cloning vector
OCRR479-OCRR480	BVH-3M	BVH-3 w/o ss (21-1039)	55	pSL301
OCRR479-OCRR497	BVH-3AD	BVH-3 N'end w/o ss (21-509)	56	pSL301
HAMJ248-HAMJ249	L-BVH-3AD	BVH-3 N'end (1-509)	57	pET-21(+)
OCRR498-OCRR499	BVH-3B	BVH-3 C'end (512-1039)	10	pSL301
OCRR479-HAMJ172	BVH-3C	BVH-3 N'end w/o ss (21-225)	59	pET-32 c(+)
OCRR487-OCRR488	BVH-11M	BVH-11 w/o ss (20-840)	60	pCMV-GH
HAMJ251-OCRR487	BVH-11A	BVH-11 N'end w/o ss (20-353)	61	pET-32 c(+)
HAMJ171-OCRR488	BVH-11B	BVH-11 C'end (354-840)	62	pET-32 a(+)
HAMJ264-OCRR488	BVH-11C	BVH-11 C'end (228-840)	63	pET-32 a(+)
HAMJ278-HAMJ279	NEW1	BVH-3 C'end (472-1039)	64	pET-21b(+)
HAMJ278-HAMJ280	NEW2	BVH-3 C'end (472-800)	65	pET-21b(+)
HAMJ281-HAMJ279	NEW3	BVH-3 C'end (800-1039)	66	pET-21b(+)
HAMJ284-HAMJ285	NEW4	BVH-11 C'end (286-840)	67	pET-21d(+)
HAMJ284-HAMJ286	NEW5	BVH-11 internal (286-713)	68	pET-21d(+)
HAMJ287-HAMJ288	NEW6	BVH-11 internal (672-792)	69	pET-21d(+)
HAMJ285-HAMJ289	NEW7	BVH-11 internal (709-840)	70	pET-21d(+)
HAMJ284-HAMJ290	NEW8	BVH-11 internal (286-511)	71	pET-21d(+)

HAMJ286-HAMJ291	NEW9	BVH-11 internal (511-713)	72	pET-21d(+)
HAMJ160-HAMJ186	BVH-11-2M	BVH-11-2 w/o ss (20-838)	73	pSL301
HAMJ292-HAMJ293	NEW10	BVH-11-2 C'end (271-838)	74	pET-21d(+)
HAMJ293-HAMJ294	NEW11	BVH-11-2 C'end (699-838)	75	pET-21d(+)
HAMJ282-HAMJ283	BVH-11B	BVH-11 C'end (354-840)	62	pET-21b(+)
HAMJ286-HAMJ297	NEW14	BVH-11-2 internal (227-699)	77	pET-21d(+)
HAMJ300-HAMJ313	NEW15	BVH-3 N'end w/o ss (21-800)	78	pET-21b(+)
HAMJ301-HAMJ302	NEW16	BVH-11 N'end w/o ss (20-709)	79	pET-21d(+)

EXAMPLE 9

This example describes the isolation of monoclonal antibodies (Mabs) and the use of Mabs to characterize BVH-3, BVH-11 and BVH-11-2 protein epitopes.

Female BALB/c mice (Charles River) were immunized subcutaneously with BVH-3, BVH-11 or BVH-11-2 gene products from S. pneumoniae strain SP64 in presence of 15 µg of QuilA adjuvant (Cedarlane Laboratories Ltd, Hornby, Canada). One set of mice (fusion experiment 1) were immunized on day 1 and 14 with 25 µg of affinity purified thioredoxin-His•Tag-BVH-3M fusion protein. A second group of mice (fusion experiment 2) were immunized three times at three-week intervals with 25 µg of affinity purified thioredoxin-His•Tag-BVH-11M. A third group of mice (fusion experiment 3) were immunized on day 1 and day 15 with 25 µg of affinity purified thioredoxin-His•Tag-BVH-11-2M fusion protein. A fourth group of mice (fusion experiment 4) were immunized on day 1 with 25 µg of affinity purified thioredoxin-His•BVH-11B fusion protein and boosted by intravenous injection on day 16 and on day 37 with recombinant BVH-11B in PBS. Three to four days before fusion, mice were injected intravenously with 25 µg of the respective antigen suspended in PBS alone. Hybridomas were produced by fusion of spleen cells with nonsecreting SP2/0 myeloma cells as previously described by J. Hamel et al. [J. Med. Microbiol., 23, pp163-170 (1987)]. Culture supernatants of hybridomas were initially screened by enzyme-linked-immunoassay according to the procedure described by Hamel et al. (Supra) using plates coated with preparations of purified recombinant proteins or suspensions of heat-killed S. pneumoniae cells. Positive hybridomas selected on the basis of ELISA reactivity with a

variety of antigens were then cloned by limiting dilutions, expanded and frozen.

Hybridomas were tested by ELISA or Western immunoblotting against BVH-3 and BVH-11 gene products in order to characterize the epitopes recognized by the Mabs. BVH-3 and BVH-11 shared common epitopes with 6 Mabs (H3-1-F9, H3-1-D4, H3-1-H12, H11-1-E7, H11-1-H10 and H11-1.1-G11) showing reactivities with both proteins (Table 4). BVH-11 and BVH-11-2 molecules from S. pneumoniae SP64 shared common epitopes not present on BVH-3 with Mabs (3A1, 13C11, 10H10, 1D8, 10G9, 10A2, 3E8, 10D7, 2H7 and 6H7) reactive with both, BVH-11 and BVH-11-2, recombinant proteins (Table 5).

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Table 4. Reactivity of BVH-3-immunoreactive Mabs with a panel of BVH-3 and BVH-11 gene products

Mabs	a. Immunoreactivity with						
	BVH-3M 21-1039	BVH-3A 21-509	BVH-3B 512-1039	BVH-3C 21-225	NEW2 472-800	NEW3 800-1039	BVH-11M 20-840
H3-1-F9	+	+	-	+	-	-	+
H3-1-D4	+	+	-	+	-	-	+
H3-1-H12	+	+	-	+	-	-	+
H3-2-G2	+	+	-	-	-	-	-
H3-3-A1	+	+	-	-	-	-	-
H3-4-D3	+	-	+	-	-	+	-
H11-1-E7	+	+	-	+	-	-	+
H11-1-H10	+	+	-	+	-	-	+
H11-1.1-G11	+	+	-	+	+	-	+

Table 5. Reactivity of Mabs raised against BVH-11-2 protein from *S. pneumoniae* strain SP64 with a panel of BVH-11 gene products

Mabs ^a	b. Immunoreactivity with							
	c. BVH-11 products				d. BVH-11-2 products			
	BVH-11M 20-840	NEW8 286-511	NEW9 511-713	BVH-11B 354-840	BVH-11-2 20-838	NEW10 271-838	NEW11 699-838	NEW14 227-699
3A1	+	+	-	+	+	+	-	+
13C1	+	+	+	+	+	+	-	+
10H10	+	+	+	+	+	+	-	+
1D8	+	+	-	+	+	+	-	+
10G9	+	-	-	+	+	+	-	+
10A2	+	-	-	+	+	+	-	+
3E8	+	-	-	+	+	+	-	+
10D7	+	-	-	+	+	+	-	+
2H7	+	-	-	-	+	-	-	-
6H7	+	-	-	-	+	-	-	-
3A4	-	-	-	-	+	+	+	-
14H6	-	-	-	-	+	+	+	-
7G2	-	-	-	-	+	+	-	+
13H10	-	-	-	-	+	-	-	+
7E8	-	-	-	-	+	-	-	-
7H6	-	-	-	-	+	-	-	-

^a Mabs listed in this table were not reactive with recombinant BVH-3 molecule

5

The results obtained from the immunoreactivity studies of the Mabs (Table 4 and Table 5) are in agreement with the protein sequences derived from the respective gene sequences. Indeed the Mabs cross-reactive with BVH-3 and BVH-11 molecules recognized BVH-3C protein corresponding to the conserved region, and BVH-11 and BVH-11-2 specific Mabs were reactive with epitopes located on variable parts of these molecules. BVH-3 and BVH-11, and BVH-11 and BVH-11-2 can be distinguished by their reactivity with Mabs.

15

EXAMPLE 10

This example illustrates the simultaneous expression of BVH-3 and BVH-11 gene products by S. pneumoniae.

A standard Western blot technique was used to investigate whether BVH-3 and BVH-11 genes were expressed in S. pneumoniae. S. pneumoniae strain SP64 and SP63 were grown overnight at 37°C in 5% CO₂ on chocolate agar plates, bacteria were suspended in PBS and heat-killed at 56°C for 20 min. For the preparation of antigens, suspensions of S. pneumoniae were treated with sample buffer containing SDS and 2-mercaptoethanol for 5 min at 100°C. Pneumococcal protein antigens were resolved by SDS-PAGE electrophoresis according to the method of Laemmli [Nature, 227, pp. 680-685 (1970)]. After SDS-PAGE, the proteins were transferred electrophoretically from the gel to nitrocellulose paper by the method of Towbin [Proc. Natl. Acad. Sci. USA, 76, pp. 4350-4354 (1979)] and probed with mouse antiserum or monoclonal antibodies. The detection of antigens reactive with the antibodies was performed by indirect enzyme-immunoassay using conjugated-anti-mouse immunoglobulins and a colour substrate. When antiserum raised to recombinant BVH-3 was tested against S. pneumoniae SP64 antigens, two reactive bands having apparent molecular masses of 127 kDa and 99 kDa were detected. Bands having the same apparent molecular masses were also detected when Mabs H3-1-F9, H3-1-D4, H3-1-H12, H11-1-E7, H11-1-H10 and H11-1.1-G11 were used individually as immunological probes. In contrast, Mabs specific for the BVH-3 molecule detected the 127 kDa band only and Mabs specific for BVH-11 detected the 99 kDa band only thus confirming the identity of the 127 and 99 kDa bands as BVH-3 and BVH-11, respectively. These studies provide evidence that BVH-3 and BVH-11 proteins are simultaneously present on S. pneumoniae. Moreover, the results are consistent with our previous observations that BVH-3 and BVH-11 possess epitopes that are common to both proteins and epitopes that are exclusive to either protein.

In S. pneumoniae SP64, mature BVH-3, BVH-11 and BVH-11-2 are proteins of 1019, 821 and 819 amino acids with predicted molecular mass of 112.5 kDa, 92.4 kDa, and 91.7 kDa, respectively. Although there is a discrepancy between the molecular mass predicted from the sequence and the molecular mass calculated on SDS-PAGE, BVH-3 can be distinguished from BVH-11 by its higher molecular mass. Moreover, BVH-3 molecules from S. pneumoniae strain SP63 have an apparent molecular mass of 112 kDa in SDS-PAGE compared to 127 kDa for BVH-3 of SP64 strain. This data is consistent with the deletion of a stretch of 177 amino acid residues in BVH-3 of S. pneumoniae strain SP63.

15

EXAMPLE 11

This example describes the protection conferred in experimental infection of mice vaccinated with recombinant BVH-3 or BVH-11 gene products.

Groups of 7 or 8 female BALB/c mice (Charles River) were immunized subcutaneously three times at three-week intervals with either affinity purified thioredoxin-His•Tag-BVH-3M fusion protein, affinity purified thioredoxin-His•Tag-BVH-11M fusion protein or, as control, with Quila adjuvant alone in PBS. Twelve to 14 days following the third immunization, the mice were challenged intravenously with S. pneumoniae WU2 strain or intranasally with P4241 strain. Samples of the S. pneumoniae challenge inoculum were plated on chocolate agar plates to determine the CFU and to verify the challenge dose. The challenge dose was approximately 10^6 CFU. Deaths were recorded for a period of 14 days and on day 14 post-challenge, the surviving mice were sacrificed and blood samples tested for

the presence of S. pneumoniae organisms. The survival data are shown in Tables 6 and 7.

5

Table 6. Protection mediated by recombinant BVH-3M and BVH-11M proteins in experimental infection with virulent S. pneumoniae WU2

Experiment	Immunogen	Alive : dead ^a	Median days alive
1	BVH-3M	8 : 0	>14
	none	0 : 8	1
2	BVH-11M	8 : 0	>14
	none	0 : 8	1

10 ^a The number of mice alive : the number of mice dead on day 14 post-challenge.

Table 7. Protection mediated by recombinant BVH-3M and BVH-11M proteins in experimental pneumonia with virulent S. pneumoniae P4241

15

Experiment	Immunogen	Alive : dead ^a	Median day alive
1	BVH-3M	6 : 1	>14
	none	1 : 7	4.5
2	BVH-3M	8 : 0	>14
	BVH-11M	8 : 0	>14
	none	0 : 8	4

^a The number of mice alive : the number of mice dead on day 14 post-challenge.

20 All mice immunized with recombinant BVH-3M or BVH-11M protein survived to infection with WU2 while none of the control mice given adjuvant alone survived. All except one mice immunized with recombinant BVH-3M or BVH-11M protein survived to infection with P4241 while only one control mice given adjuvant alone survived. All hemocultures from

surviving mice were negative at day 14 post-challenge. These results clearly indicate that both, BVH-3M and BVH-11M, elicit protective anti-pneumococcal immune responses in mice. The fact that these proteins are highly conserved among S. pneumoniae isolates emphasize the potential of BVH-3 and BVH-11 as universal vaccine candidates. Indeed, the BVH-3 and BVH-11 proteins from serogroup 6 S. pneumoniae strain SP64 elicited protection against pneumococcal infections with strains of different capsular serotypes.

Ideally, a vaccine that could protect against pneumococcal disease, could protect against meningitis, otitis media, bacteremia and pneumonia. BVH-3 and BVH-11 were protective against lethal systemic- and pneumonia-infection models thus suggesting that, in humans, BVH-3- and BVH11-protein-based vaccines could reduce the incidence of a wide spectrum of disease caused by virtually all S. pneumoniae independently of the capsular serotype.

Data from Tables 6 and 7 clearly demonstrate that BVH-3 and BVH-11 were, both, protection-eliciting molecules of S. pneumoniae. It was not known, however, whether protection can be mediated by specific sequences that were not shared on BVH-3 and BVH-11 molecules. Groups of female BALB/c mice (Charles River) were immunized subcutaneously three times at three-week intervals with either affinity purified thioredoxin-His•Tag- BVH-3AD, -BVH-3B or -BVH-3C fusion protein in presence of 15 µg of QuilA adjuvant (Cedarlane Laboratories Ltd, Hornby, Canada). Control mice were immunized with QuilA adjuvant alone in PBS or affinity purified thioredoxin-His•Tag or thioredoxin-His•Tag-fusion protein (His-Thio) in presence of QuilA.

To determine the protective ability of a set of truncated proteins, termed NEW4, NEW5, NEW6, NEW7, NEW8, NEW9, NEW10,

NEW11, NEW14 and BVH-11B, groups of female BALB/c mice (Charles River) were immunized subcutaneously two times at three-week intervals with 25 μ g of either affinity purified His•Tag-fusion protein in presence of 15 μ g of QuilA
5 adjuvant. Ten to 14 days following the last immunization, the mice were challenged with virulent S. pneumoniae. Our results indicate that, BVH-3B, a truncated BVH-3 molecule consisting of amino acids 512-1039, elicited protection against the mouse-virulent strains WU2 and P4241.
10 Similarly, BVH-11B, NEW4 and NEW5 molecules, three truncated BVH-11 molecules consisting of amino acids 354-840, amino acids 286-840 and amino acids 286-713, respectively, elicited protection against experiment intravenous challenge with WU2 and intranasal challenge
15 with P4241. Moreover, vaccination with NEW10 and NEW14, consisting of amino acids 272-838 and amino acids 227-699 from BVH-11-2 molecule also resulted in protection against death with the pneumococcal strains. These results indicate that the region comprising 428 amino acids
20 extending from amino acids 286-713 and amino acids 272-699 on S. pneumoniae SP64 BVH-11 and BVH-11-2 protein sequences, respectively, contains protective epitopes. This region is highly conserved with a global 91% identity and 94% homology among thirteen BVH-11 protein sequences.
25

Table 8. Evaluation of protection elicited by vaccination of mice with BVH-3 and BVH-11 gene products

Experiment	Immunogen	Challenge with WU2		Challenge with P4241	
		Alive : dead ^a	Median day alive	Alive : dead	Median day alive
1 ^b	None	0 : 8	1.5	1 : 7	4.5
	NEW4	8 : 0	>14	8 : 0	>14
	NEW5	8 : 0	>14	8 : 0	>14
	NEW7	0 : 8	2	0 : 8	5
	BVH-11M	8 : 0	>14	8 : 0	>14
2 ^b	None	0 : 8	1	0 : 8	4
	NEW5	8 : 0	>14	8 : 0	>14
	NEW8	0 : 8	1.5	0 : 8	5.5
	NEW9	3 : 5	3.5	2 : 6	7
	BVH-11M	8 : 0	>14	8 : 0	>14
3 ^b	None	0 : 8	1	0 : 8	4
	NEW6	0 : 8	1	4 : 4	10.5 ^c
	NEW10	8 : 0	>14	8 : 0	>14
	NEW11	0 : 8	1.5	1 : 7	6
	BVH-11M	8 : 0	>14	8 : 0	>14
4 ^b	None	0 : 8	2	0 : 8	4
	BVH-11B	7 : 1	>14	8 : 0	>14
	NEW14	8 : 0	>14	8 : 0	>14
5	His-Thio	0 : 8	2		
	BVH-3AD	1 : 7	2.5		
	BVH-3B	5 : 3	>14		
6	His-Thio	0 : 8	1		
	BVH-3C	0 : 8	1		

^a The number of mice alive : the number of mice dead on day 14 post-challenge.

5 ^b The WU2 challenge dose was 10⁵ CFU.

^c Mice living longer than 14 days were assigned a survival time of 14 days for the determination of median values.

EXAMPLE 12

5 This example described the cloning and expression of a
chimeric gene encoding for a chimeric polypeptide
corresponding to the carboxy-terminal region of BVH-3 in
fusion at the C' end to the carboxy-terminal region of BVH-
11 and the additive protection observed after vaccination
with a chimeric polypeptide.

10

It is clear from the studies described above that BVH-3 and
BVH-11 are serologically distinct molecules simultaneously
present on S. pneumoniae. The results of immunological
studies of mice indicate that both proteins are good
15 vaccine candidates. These proteins have the potential to
provide protection against all pneumococci, regardless of
serotype. Even though the two proteins share epitopes and
sequences, they have different characteristics and may
serve different biological functions. Thus, immunization
20 against the two proteins may provide a higher level of
protection than that imparted by each individually. To
examine this, several avenues where full-length or
truncated BVH-3 and BVH-11 are administered in combination
or in conjugation can be explored. Here we describe the
25 genetic engineering of a BVH-3-BVH-11 fusion gene and
protein, termed NEW12 (SEQ ID NO:76 and SEQ ID NO:58,
respectively), and the potential use of NEW12 protein as a
vaccine.

30 BVH-3 and BVH-11 gene fragments corresponding to the 3' end
of the genes were amplified by PCR using pairs of
oligonucleotides engineered to amplify fragments spanning
nucleotides 1414 to 3117 (SEQ ID NO: 1) and nucleotides 1060
to 2520 (SEQ ID NO: 3) from S. pneumoniae strain SP64 BVH-3
35 and BVH-11 genes, respectively. The primers used, HAMJ278
and HAMJ279; HAMJ282 and HAMJ283 had a restriction

endonuclease site at the 5' end, thereby allowing directional in-frame cloning of the amplified product into the digested pET21b(+) plasmid vector (Table 2). PCR-amplified products were digested with restriction
5 endonucleases and ligated to linearized plasmid pET21b(+) vector digested likewise. The resultant plasmid constructs were confirmed by nucleotide sequence analysis. The recombinant pET21b(+) plasmid containing the NdeI-HindIII BVH-3 PCR product was linearized by digestion with the
10 restriction enzymes HindIII and NotI for the in-frame cloning of the HindIII-NotI DNA fragment obtained from the recombinant pET21(+) vector containing the BVH-11 gene fragment. Clones were first stabilized in E. coli DH5 α before introduction into E. coli BL21(λ DE3) for expression
15 of a chimeric pneumococcal protein molecule. The recombinant chimeric polypeptide, termed NEW 12, was expressed as C-terminal fusion with an His-tag. The expressed recombinant NEW 12 protein was purified from supernatant fractions obtained from centrifugation of
20 sonicated IPTG-induced E. coli cultures using a His-Bind metal chelation resin (QIAGEN, Chatsworth, CA).

According to the same procedure described above, it is possible to construct other chimeric polypeptides, as a
25 result of a simultaneous expression of New 1 and New 4, New 1 and New 5, New 1 and New 10, or New 1 and New 14. The construction can be with New 1 upstream or downstream of New 4, New 5, New 10, BVH-11B or New 14. It is also possible to construct other chimeric polypeptides as a
30 result of a simultaneous expression of more than two fragments of either genes of BVH-3, BVH-11 or BVH-11-2.

Groups of 8 female BALB/c mice (Charles River) were immunized subcutaneously two times at three-week intervals
35 with 25 μ g of either affinity purified His•Tag-fusion NEW1,

BVH-11B or NEW12 protein in presence of 15 μ g of QuilA adjuvant. Ten to 14 days following the last immunization, the mice were challenged with virulent *S. pneumoniae*. As demonstrated before, NEW1 and BVH-11B molecules comprising amino acids 472 to 1039 from BVH-3 protein and amino acids 354-840 from BVH-11 protein, respectively, correspond to portions of the proteins capable of eliciting a protective immune response. To determine if a chimeric polypeptide would significantly improve the protection compared with those seen for the individual counterparts, the challenge dose was adjusted in a manner that protection was not expected with NEW1 and BVH-11B molecules. Interestingly, the chimeric NEW12 protein, elicited protection against the mouse-virulent strains WU2 and P4241. Seven out of 8 mice immunized with NEW12 were still alive 10 days after the challenge while 28 out of 32 mice immunized with NEW1, BVH-11B, BVH-3M or adjuvant alone were dead by five days post-challenge. Thus, vaccination of mice with NEW12 provided the highest degree of protection against WU2 challenge. These results indicate that immunization with a chimeric polypeptide and possibly a combination of BVH-3 and BVH-11 gene products can provide additional protection to that obtained by administration of BVH-3 or BVH-11 antigens alone.

Table 9. Evaluation of protection elicited by vaccination of mice with the chimeric NEW12 molecule

Immunogen	Challenge with WU2		Challenge with P4241	
	Alive : dead ^a	Median day alive	Alive : dead	Median day alive
None	0 : 8	1	0 : 8	5
NEW1	2 : 6	2	1 : 7	8
BVH-11B	1 : 7	3.5	8 : 0	>14
NEW12	6 : 2	>14	7 : 1	>14
BVH-3M	1 : 7	3	8 : 1	>14

EXAMPLE 13

5

This example illustrates the identification of additional BVH-3 and BVH-11 related sequences in Streptococcus species other than S. pneumoniae.

- 10 It was previously shown that BVH-3, BVH-11 and BVH-11-2 are a family of related proteins sharing common sequences. Homology searches were performed with the nucleotide sequence from the conserved region of these genes and compared with GenBank and EMBL sequences using FASTA. The
- 15 most significant homology was observed with a 2.469-kb gene coding for a calculated 92-kDa protein (**SEQ ID NO: 81**) of unknown function in S. agalactiae also called group B streptococcus or GBS. The gene was designated BVH-71. A protein demonstrating 99.2% identity and 99.5% similarity
- 20 with that of GBS was also identified in S. pyogenes also called group A streptococcus or GAS (**SEQ ID NO: 83**). The 5' region of the BVH-71 sequences (**SEQ ID NO: 80** and **SEQ ID NO: 82**), spanning nucleotides 1 to 717, demonstrated 58 and 60% identity with the conserved regions of BVH-3
- 25 (nucleotides 1 to 675) and BVH-11 (nucleotides 1 to 684) genes respectively. The first 239 amino acids of the translated sequences of the GBS and GAS BVH-71 open reading frames are 51 and 54% identical to the first 225 and 228 amino acids of BVH-3 and BVH-11, respectively. In addition
- 30 to structural similarities, streptococcal BVH-3, BVH-11 and BVH-71 proteins also share antigenic epitopes. A 97-kDa band was revealed on Western blots of GAS or GBS whole cells, using Mab H11-1.1-G11 reactive with the BVH-3 and BVH-11 conserved regions. Similarly, GAS and GBS

recombinant BVH-71 proteins were detected in Western immunoblot analysis.

These results indicate that BVH-71, BVH-3 and BVH-11 proteins might share similar functions. Our results also
5 suggest that BVH-71 proteins can be used as protein vaccine components of anti-streptococcus. In a further embodiment BVH-71 proteins can be used as protein vaccine components of anti-GAS or anti-GBS vaccines.

What is claimed is:

1. An isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide having a sequence chosen from: SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.
2. A polynucleotide according to claim 1, wherein said polynucleotide encodes a polypeptide having at least 95% identity to the second polypeptide.
3. An isolated polynucleotide encoding a polypeptide capable of generating antibodies having binding specificity for a polypeptide having a sequence chosen from: SEQ ID NOs: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.
4. An isolated polynucleotide that is complementary to the polynucleotide of claim 1.
5. An isolated polynucleotide that is complementary to the polynucleotide of claim 3.
6. The polynucleotide of claim 1, wherein said polynucleotide is DNA.
7. The polynucleotide of claim 3, wherein said polynucleotide is DNA.
8. The polynucleotide of claim 1, wherein said polynucleotide is RNA.
9. The polynucleotide of claim 3, wherein said polynucleotide is RNA.

10. A vector comprising the polynucleotide of claim 1, wherein said DNA is operably linked to an expression control region.
11. A vector comprising the polynucleotide of claim 3, wherein said DNA is operably linked to an expression control region.
12. A host cell transfected with the vector of claim 10.
13. A host cell transfected with the vector of claim 11.
14. A process for producing a polypeptide comprising culturing a host cell according to claim 12 under conditions suitable for expression of said polypeptide.
15. A process for producing a polypeptide comprising culturing a host cell according to claim 13 under condition suitable for expression of said polypeptide.
16. An isolated polypeptide having at least 70% identity to a second polypeptide having an amino acid sequence chosen from: SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.
17. An isolated polypeptide capable of generating antibodies having binding specificity for a second polypeptide having a sequence chosen from: SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.
18. An isolated polypeptide having an amino acid sequence chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

19. An isolated polypeptide according to claim 18, wherein the N-terminal Met residue is deleted.
20. An isolated polypeptide according to claim 18, wherein the secretory amino acid sequence is deleted.
21. A chimeric polypeptide comprising two or more polypeptides chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof; provided that the polypeptides or fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.
22. A chimeric polypeptide comprising two or more polypeptides chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof; provided that the polypeptides or fragments, analogs or derivatives thereof are linked as to form a chimeric polypeptide.
23. A chimeric polypeptide of formula (I):
A-(B)_m-(C)_n-D (I)
Wherein;
m is 0 or 1,
n is 0 or 1,
A is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof;
B is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof;
C is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55 to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof; and
D is chosen from SEQ ID NOS: 2, 4, 6, 8, 10, 14, 16, 55

to 75, 77 to 79, 81, 83 or fragments, analogs or derivatives thereof.

24. A chimeric polypeptide of formula (I):
 $A-(B)_m-(C)_n-D$ (I)
Wherein;
 m is 0 or 1,
 n is 0 or 1,
 A is chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof;
 B is chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77, or fragments, analogs or derivatives thereof;
 C is chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof; and
 D is chosen from SEQ ID NOS :10, 58, 60, 62, 64, 67, 68, 69, 72, 74, 77 or fragments, analogs or derivatives thereof.
25. A vaccine composition comprising a polypeptide according to any one of claims 16 to 24 and a pharmaceutically acceptable carrier, diluent or adjuvant.
26. A method for therapeutic or prophylactic treatment of meningitis, otitis media, bacteremia or pneumonia infection in an individual susceptible to meningitis, otitis media, bacteremia or pneumonia infection comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 25.
27. A method for therapeutic or prophylactic treatment of streptococcal bacterial infection in an individual

susceptible to streptococcal infection comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 25.

28. A method according to claim 26, wherein said individual is a mammal.
29. A method according to claim 27, wherein said individual is a human.
30. A method according to claim 22, wherein said bacterial infection is S.pneumoniae, group A streptococcus (pyogenes), group B streptococcus (GBS or agalactiae), dysgalactiae, uberis, nocardia or Staphylococcus aureus.
31. A method according to claim 26, wherein said bacterial infection is S.pneumoniae.
32. Use of a vaccine composition according to claim 25 for the prophylactic or therapeutic treatment of Streptococcal infection in an animal susceptible to or infected with streptococcal infection comprising administering to said animal a prophylactic or therapeutic amount of the composition.

ATGAAATTTA	GTAAAAAATA	TATAGCAGCT	GGATCAGCTG	TTATCGTATC	CTTGAGTCTA	60
TGTGCCTATG	CACTAAACCA	GCATCGTTTC	CAGGAAAATA	AGGACAATAA	TCGTGTCTCT	120
TATGTGGATG	GCAGCCAGTC	AAGTCAGAAA	AGTGAAAAC	TGACACCAGA	CCAGGTTAGC	180
CAGAAAGAAG	GAATTCAGGC	TGAGCAAATT	GTAATCAAAA	TTACAGATCA	GGGCTATGTA	240
ACGTCACACG	GTGACCACTA	TCATTACTAT	AATGGGAAAG	TTCTTATGA	TGCCCTCTTT	300
AGTGAAGAAC	TCTTGATGAA	GGATCCAAAC	TATCAACTTA	AAGACGCTGA	TATTGTCAAT	360
GAAGTCAAGG	GTGGTTATAT	CATCAAGGTC	GATGGAAAAT	ATTATGTCTA	CCTGAAAGAT	420
GCAGCTCATG	CTGATAATGT	TCGAACTAAA	GATGAAATCA	ATCGTCAAAA	ACAAGAACAT	480
GTCAAAGATA	ATGAGAAGGT	TAACTCTAAT	GTTGCTGTAG	CAAGGTCTCA	GGGACGATAT	540
ACGACAAATG	ATGGTTATGT	CTTTAATCCA	GCTGATATTA	TCGAAGATAC	GGGTAATGCT	600
TATATCGTTC	CTCATGGAGG	TCACTATCAC	TACATTCCCA	AAAGCGATTT	ATCTGCTAGT	660
GAATTAGCAG	CAGCTAAAGC	ACATCTGGCT	GGAAAAATA	TGCAACCGAG	TCAGTTAAGC	720
TATTCTTCAA	CAGCTAGTGA	CAATAACACG	CAATCTGTAG	CAAAAGGATC	AACTAGCAAG	780
CCAGCAAATA	AATCTGAAAA	TCTCCAGAGT	CTTTTGAAGG	AACTCTATGA	TTCACCTAGC	840
GCCCAACGTT	ACAGTGAATC	AGATGGCCTG	GTCTTTGACC	CTGCTAAGAT	TATCAGTCGT	900
ACACCAAATG	GAGTTGCGAT	TCCGCATGGC	GACCATTACC	ACTTTATTCC	TTACAGCAAG	960
CTTTCTGCTT	TAGAAGAAAA	GATTGCCAGA	ATGGTGCCTA	TCAGTGGAAC	TGGTTCTACA	1020
GTTTCTACAA	ATGCAAAACC	TAATGAAGTA	GTGCTAGTTC	TAGGCACTCT	TTCAAGCAAT	1080
CCTTCTTCTT	TAACGACAAG	TAAGGAGCTC	TCTTCAGCAT	CTGATGGTTA	TATTTTAAAT	1140
CCAAAAGATA	TCGTTGAAGA	AACGGCTACA	GCTTATATTG	TAAGACATGG	TGATCATTTT	1200
CATTACATTC	CAAAATCAAA	TCAAATTGGG	CAACCGACTC	TTCCAAACAA	TAGTCTAGCA	1260
ACACCTTCTC	CATCTCTTCC	AATCAATCCA	GGAACTTCAC	ATGAGAAACA	TGAAGAAGAT	1320
GGATACGGAT	TTGATGCTAA	TCGTATTATC	GCTGAAGATG	AATCAGGTTT	TGTCATGAGT	1380
CACGGAGACC	ACAATCATT	TTTCTTCAAG	AAGGACTTGA	CAGAAGAGCA	AATTAAGGCT	1440
GCGCAAAAC	ATTTAGAGGA	AGTTAAACT	AGTCATAATG	GATTAGATTTC	TTTGTCATCT	1500
CATGAACAGG	ATTATCCAGG	TAATGCCAAA	GAAATGAAAG	ATTAGATAA	AAAAATCGAA	1560
GAAAAAATTG	CTGGCATTAT	GAAACAATAT	GGTGTCAAAC	GTGAAAGTAT	TGTCGTGAAT	1620
AAAGAAAAAA	ATGCGATTAT	TTATCCGCAT	GGAGATCACC	ATCATGCAGA	TCCGATTGAT	1680
GAACATAAAC	CGGTTGGAAT	TGGTCATTCT	CACAGTAACT	ATGAACTGTT	TAAACCCGAA	1740
GAAGGAGTGT	CTAAAAAAGA	AGGGAATAAA	GTTTATACTG	GAGAAGAATT	AACGAATGTT	1800
GTTAATTTGT	TAAAAAATAG	TACGTTTAAT	AATCAAAACT	TTACTCTAGC	CAATGGTCAA	1860
AAACGCGTTT	CTTTTAGTTT	TCCGCTTGAA	TTGGAGAAAA	AATTAGGTAT	CAATATGCTA	1920
GTAAATTTAA	TAACACCAGA	TGGAAGAGTA	TTGGAGAAAG	TATCTGGTAA	AGTATTTGGA	1980
GAAGGAGTAG	GGAATATTGC	AAACTTTGAA	TTAGATCAAC	CTTATTTACC	AGGACAAACA	2040
TTTAAGTATA	CTATCGCTTC	AAAAGATTAT	CCAGAAGTAA	GTTATGATGG	TACATTTACA	2100
GTTCCAACCT	CTTTAGCTTA	CAAAATGGCC	AGTCAAACGA	TTTTCTATCC	TTTCCATGCA	2160
GGGATACTTT	ATTTAAGAGT	GAACCCTCAA	TTTGCACTGC	CTAAAGGAAC	TGATGCTTTA	2220
GTCAAGAGTG	TTGATGAATT	TCATGGAAAT	GCTTATTTAG	AAAATAACTA	TAAAGTTGGT	2280
GAAATCAAAT	TACCGATTCC	GAAATTAAC	CAAGGAACAA	CCAGAACGGC	CGGAAATAAA	2340
ATTCCTGTAA	CCTTCATGGC	AAATGCTTAT	TTGGACAATC	AATCGACTTA	TATTGTGGAA	2400
GTACCTATCT	TGGAAGAAAG	AAATCAAAC	GATAAACCAA	GTATTCTACC	ACAATTTAAA	2460
AGGAATAAAG	CACAAGAAAA	CTCAAACTT	GATGAAAAGG	TAGAAGAAC	AAAGACTAGT	2520
GAGAAGGTAG	AAAAAGAAAA	ACTTTCTGAA	ACTGGGAATA	GTACTAGTAA	TTCAACGTTA	2580
GAAGAAGTTC	CTACAGTGGA	TCCTGTACAA	GAAAAAGTAG	CAAAATTTGC	TGAAAGTTAT	2640
GGGATGAAGC	TAGAAAATGT	CTTGTTTAAAT	ATGGACGGAA	CAATTGAATT	ATATTTACCA	2700
TCAGGAGAAG	TCATTAAAAA	GAATATGGCA	GATTTTACAG	GAGAAGCACC	TCAAGGAAAT	2760
GGTGAAAATA	AACCATCTGA	AAATGGAAAA	GTATCTACTG	GAACAGTTGA	GAACCAACCA	2820
ACAGAAAATA	AACCAGCAGA	TTCTTTACCA	GAGGCACCAA	ACGAAAAACC	TGTAAAACCA	2880
GAAAACTCAA	CGGATAATGG	AATGTTGAAT	CCAGAAGGGA	ATGTGGGGAG	TGACCCTATG	2940
TTAGATCCAG	CATTAGAGGA	AGCTCCAGCA	GTAGATCCTG	TACAAGAAAA	ATTAGAAAAA	3000
TTTACAGCTA	GTTACGGATT	AGGCTTAGAT	AGTGTTATAT	TCAATATGGA	TGGAACGATT	3060
GAATTAAGAT	TGCCAAGTGG	AGAAGTGATA	AAAAAGAATT	TATCTGATTT	CATAGCGTAA	3120

(SEQ ID NO: 1)

FIGURE 1

MKFSKKYIAA	GSAVIVLSL	CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	50
SENLTDPQVS	QKEGIQAEQI	VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	100
SEELLMKDPN	YQLKDADIVN	EVKGGYIIKV	DGKYVYVLKD	AAHADNVRTK	150
DEINRQKQEH	VKDNEKVNSN	VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	200
YIVPHGGHYH	YIPKSDLSAS	ELAAAKAHLA	GKNMQPSQLS	YSSTASDNNT	250
QSVAKGSTSK	PANKSENLSQ	LLKELYDSPA	AQRYSESDGL	VFDPAKIISR	300
TPNGVAIPHG	DHYHFIPYSK	LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	350
VSSLGSLSSN	PSSLTTSKEL	SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	400
HYIPKSNQIG	QPTLPNNSLA	TPSPSLPINP	GTSHEKHEED	GYGFDANRII	450
AEDESGFVMS	HGDHNHYFFK	KDLTEEQIKA	AQKHLEEVKT	SHNGLDLSS	500
HEQDYPGNAK	EMKDLDKKIE	EKIAGIMKQY	GVKRESIVVN	KEKNAIYPH	550
GDHHHADPID	EHKPVGIGHS	HSNYELFKPE	EGVAKKEGK	VYTGEELTNV	600
VNLLKNSTFN	NQNFTLANGQ	KRVSFSPPE	LEKKLGINML	VKLITPDGKV	650
LEKVSQKVPF	EGVGNIANFE	LDQPYLPGQT	FKYTIASKDY	PEVSYDGTFT	700
VPTSLAYKMA	SQTIFFPFHA	GDTYLRVNPQ	FAVPKGTDAL	VRVFDEFHGN	750
AYLENNYKVG	EIKLPIPKLN	QGTTRTAGNK	IPVTFMANAY	LDNQSTYIVE	800
VPILEKENQT	DKPSILPQFK	RNKAQENSKL	DEKVEEPKTS	EKVEKEKLSE	850
TGNSTSNSTL	EEVPTVDPVQ	EKVAKFAESY	GMKLENVLFN	MDGTIELYLP	900
SGEVIKKNMA	DFTGEAPQGN	GENKPSENGK	VSTGTVENQP	TENKPADSLP	950
EAPNEKPKVP	ENSTDNGMLN	PEGNVGSDPM	LDPAL EEAPA	VDPVQEKLEK	1000
FTASYGLGLD	SVIFNMGTI	ELRLPSGEVI	KKNLSDFIA	(SEQ ID NO: 2)	1039

FIGURE 2

ATGAAAATCA	ATAAAAAATA	TCTAGCTGGG	TCAGTAGCTA	CACTTGTTTT	AAGTGTCTGT	60
GCTTATGAAC	TAGGTTTGCA	TCAAGCTCAA	ACTGTAAAG	AAAATAATCG	TGTTTCCTAT	120
ATAGATGGAA	AACAAGCGAC	GCAAAAAACG	GAGAATTTGA	CTCCTGATGA	GGTTAGCAAG	180
CGTGAAGGAA	TCAACGCCGA	ACAAATCGTC	ATCAAGATTA	CGGATCAAGG	TTATGTGACC	240
TCTCATGGAG	ACCATTATCA	TTACTATAAT	GGCAAGGTCC	CTTATGATGC	CATCATCAGT	300
GAAGAGCTCC	TCATGAAAGA	TCCGAATTAT	CAGTTGAAGG	ATTCAGACAT	TGTCAATGAA	360
ATCAAGGGTG	GTTATGTCAT	TAAGGTAAAC	GGTAAATACT	ATGTTTACCT	TAAGGATGCA	420
GCTCATGCGG	ATAATGTCCG	TACAAAAGAA	GAAATCAATC	GGCAAAAACA	AGAACATAGT	480
CAGCATCGTG	AAGGAGGGAC	TTCAGCAAAC	GATGGTGCGG	TAGCCTTTGC	ACGTTCCACAG	540
GGACGCTACA	CCACAGATGA	TGGTTATATC	TTCAATGCAT	CTGATATCAT	CGAAGATACG	600
GGCGATGCCT	ATATCGTTCC	TCATGGAGAT	CATTACCATT	ACATTCTCTAA	GAATGAGTTA	660
TCAGCTAGCG	AGTTGGCTGC	TGCAGAAGCC	TTCTATCTGT	GTCGGGAAAA	TCTGTCAAAT	720
TTAAGAACCT	ATCGCCGACA	AAATAGCGAT	AACACTCCAA	GAACAACTG	GGTACCTTCT	780
GTAAGCAATC	CAGGAACACT	AAATACTAAC	ACAAGCAACA	ACAGCAACAC	TAACAGTCAA	840
GCAAGTCAAA	GTAATGACAT	TGATAGTCTC	TTGAAACAGC	TCTACAAACT	GCCTTTGAGT	900
CAACGCCATG	TAGAATCTGA	TGGCCTTATT	TTCCGACCCAG	CGCAAATCAC	AAGTCGAACC	960
GCCAGAGGTG	TAGCTGTCCC	TCATGGTAAC	CATTACCACT	TTATCCCTTA	TGAACAAATG	1020
TCTGAATTGG	AAAAACGAAT	TGCTCGTATT	ATTCCCCCTC	GTTATCGTTC	AAACCATTGG	1080
GTACCAGATT	CAAGACCAGA	AGAACCAAGT	CCACAACCGA	CTCCAGAACC	TAGTCCAAGT	1140
CCGCAACCTG	CACCAAATCC	TCAACCAGCT	CCAAGCAATC	CAATTGATGA	GAAATTGGTC	1200
AAAGAAGCTG	TTCGAAAAGT	AGGCGATGGT	TATGTCTTTG	AGGAGAATGG	AGTTTCTCGT	1260
TATATCCAG	CCAAGAATCT	TTCAGCAGAA	ACAGCAGCAG	GCATTGATAG	CAAACCTGGCC	1320
AAGCAGGAAA	GTTTATCTCA	TAAGCTAGGA	GCTAAGAAAA	CTGACCTCCC	ATCTAGTGAT	1380
CGAGAATTTT	ACAATAAGGC	TTATGACTTA	CTAGCAAGAA	TTCACCAAGA	TTTACTTGAT	1440
AATAAAGGTC	GACAAGTTGA	TTTTGAGGCT	TTGGATAACC	TGTTGGAACG	ACTCAAGGAT	1500
GTCTCAAGTG	ATAAAGTCAA	GTTAGTGGAT	GATATTCTTG	CCTTCTTAGC	TCCGATTTCGT	1560
CATCCAGAAC	GTTTAGGAAA	ACCAAATGCG	CAAATTACCT	ACACTGATGA	TGAGATTCAA	1620
GTAGCCAAGT	TGGCAGGCAA	GTACACAACA	GAAGACGGTT	ATATCTTTGA	TCCTCGTGAT	1680
ATAACCAGTG	ATGAGGGGGA	TGCCTATGTA	ACTCCACATA	TGACCCATAG	CCACTGGATT	1740
AAAAAAGATA	GTTTGTCTGA	AGCTGAGAGA	GCGGCAGCCC	AGGCTTATGC	TAAAGAGAAA	1800
GGTTTGACCC	CTCCTTCGAC	AGACCATCAG	GATTTCAGGAA	ATACTGAGGC	AAAAGGAGCA	1860
GAAGCTATCT	ACAACCGCGT	GAAAGCAGCT	AAGAAGGTGC	CACCTGATCG	TATGCCTTAC	1920
AATCTTCAAT	ATACTGTAGA	AGTCAAAAAC	GGTAGTTTAA	TCATACCTCA	TTATGACCAT	1980
TACCATAACA	TCAAATTTGA	GTGGTTTGAC	GAAGGCCTTT	ATGAGGCACC	TAAGGGGTAT	2040
ACTCTTGAGG	ATCTTTTGCC	GACTGTCAAG	TACTATGTCTG	AACATCCAAA	CGAACGTCCG	2100
CATTGAGATA	ATGGTTTTGG	TAACGCTAGC	GACCATGTTT	AAAGAAACAA	AAATGGTCAA	2160
GCTGATACCA	ATCAAACGGA	AAAACCAAGC	GAGGAGAAAC	CTCAGACAGA	AAAACCTGAG	2220
GAAGAAACCC	CTCGAGAAGA	GAAACCACAA	AGCGAGAAAC	CAGAGTCTCC	AAAACCAACA	2280
GAGGAACCCG	AAGAAGAATC	ACCAGAGGAA	TCAGAAGAAC	CTCAGGTCTGA	GACTGAAAAG	2340
GTTGAAGAAA	AACTGAGAGA	GGCTGAAGAT	TTACTTGGAA	AAATCCAGGA	TCCAATTATC	2400
AAGTCCAATG	CCAAAGAGAC	TCTCACAGGA	TTAAAAATA	ATTTACTATT	TGGCACCCAG	2460
GACAACAATA	CTATTATGGC	AGAAGCTGAA	AAACTATTGG	CTTTATTAAA	GGAGAGTAAG	2520
TAA (SEQ ID NO: 3)						2523

FIGURE 3

MKINKKYL	AG SVATLVL	SVC AYELGL	HQAO TVKENN	RVSY IDGK	QATQKT	50			
ENLTPDEV	SK REGINAE	QIV IKITDQ	GYVT SHGD	DHYHYN	GKVPYDAIIS	100			
EELLMKDP	NY QLKDS	DIVNE IKG	GYVIKVN	GKYYVYL	KDA AHADNV	RTKE 150			
EINRQKQEH	S QHREGG	TAN DGAVAF	ARSQ GR	YTTDDGYI	FNASDI	IEDT 200			
GDAYIVPH	GD HYHYI	PKNEL SASE	LAAAEA	FLSGREN	LSN LR	TYRRQNSD 250			
NTPRTN	WVPS VSNP	GTTNTN	TSNNSNT	NSQ ASQ	SNDIDSL	LKQLYKLPLS 300			
QRHVESDGLI	FDPAQIT	SRT ARGV	AVPHGN	HYHFI	PYEQM SELE	KRIARI 350			
IPLRYR	SNHW VPDS	RPEEPS	PQPTPE	SPS PQ	PAPNPQPA	PSNPIDEKLV 400			
KEAVRK	VGDG YVFE	ENGVS	R YIPAK	NLSAE	TAAGID	SKLA KQESL	SHKLG 450		
AKKTDLPSSD	REFYNK	AYDL LARI	HQDLLD	NKGRQ	VD	FEA LDNLL	LERLKD 500		
VSSDKVKLVD	DILAF	LAPIR HPER	L	GKPN	A QITYT	DDEIQ	VAKLAGKYTT 550		
EDGYIFDPRD	ITSDEG	DAYV TPHM	THSHWI	KKDSL	SEAER	AAAQAY	AKEK 600		
GLTPPSTDHQ	DSGNTE	AKGA EAIY	NRVKA	A KKVPL	DRMPY	NLQYT	VEVKN 650		
GSLIIPHYDH	YHNIK	FEWFD EGLY	EAPKGY	TLEDL	LATVK	YYVEH	PNERP 700		
HSDNGFGNAS	DHVQR	NKNGQ	ADTNQ	TEKPS	EEKPQ	TEKPE	EETPRE	EKPQ 750	
SEKPESPKPT	EEPEE	ESPEE	SEEPQ	VETEK	VEEK	LREAED	LLGKI	QDP	II 800
KSNAKETLTG	LKNLL	FGTQ DNNT	IMAEAE	KLLALL	KESK	(SEQ ID NO: 4)	840		

FIGURE 4

ATGGAGAATA	TAGACATGTT	TAAATCAAAT	CATGAGCGAA	GAATGCGTTA	TTCCATTTCGT	60
AAATTTAGTG	TAGGAGTAGC	TAGCGTAGCT	GTGCGCAGTC	TTTTTATGGG	AAGTGTGTGA	120
CATGCGACAG	AGAAAGAGGG	AAGTACCCAA	GCAGCCACTT	CTTTTAATAG	GGGAAATGGA	180
AGTCAGGCAG	AACAACGTGG	AGAACTCGAT	TTAGAACGAG	ATAAGGCAAT	GAAAGCGGTC	240
AGTGAATATG	TAGGAAAAAT	GGTGAGAGAT	GCCTATGTAA	AATCAGATAG	AAAACGACAT	300
AAAAATACTG	TAGCTCTAGT	TAACCAGTTG	GGAAACATTA	AGAACAGGTA	TTTGAATGAA	360
ATAGTTCATT	CAACCTCAAA	AAGCCAACTA	CAGGAACTGA	TGATGAAGAG	TCAATCAGAA	420
GTAGATGAAG	CTGTGTCTAA	ATTTGAAAAG	GACTCATTTT	CTTCGTCAAG	TTCAGGATCC	480
TCCACTAAAC	CAGAAACTCC	GCAGCCGGAA	AATCCAGAGC	ATCAAAAACC	AACAACCTCCA	540
TCTCCGGATA	CCAAAACCAAG	CCCTCAACCA	GAAGGCAAGA	AACCAAGCGT	ACCAGACATT	600
AATCAGGAAA	AAGAAAAAGC	TAAGCTTGCT	GATGTAACCT	ACATGAGCAA	GATTTTATAGT	660
GATATACAAA	AACATCATCT	GCAGAAAGAA	AAACATCGTC	AGATTGTTGC	TCTTATTAAG	720
GAGCTTGATG	AGCTTAAAAA	GCAAGCTCTT	TCTGAAATTG	ATAATGTAAA	TACCAAAGTA	780
GAAATTGAAA	ATACAGTCCA	CAAGATATTT	GCAGACATGG	ATGCAGTTGT	GACTAAATTC	840
AAAAAAGGCT	TAACCTCAGGA	CACACCAAAA	GAACCAGGTA	ACAAAAAACC	ATCTGCTCCA	900
AAACCAGGTA	TGCAACCAAG	TCCTCAACCA	GAGGTAAAC	CGCAGCTGGA	AAAACCAAAA	960
CCAGAGGTTA	AACCGCAACC	AGAAAAACCA	AAACCAGAGG	TTAAACCGCA	GCCGGAAAAA	1020
CCAAAACCCAG	AGGTAAAC	GCAGCCGGAA	AAACCAAAAC	CAGAGGTTAA	ACCGCAGCCG	1080
GAAAAACCAA	AACCAGAGGT	TAAACCGCAG	CCGGAAAAAC	CAAAACCAGA	GGTTAAACCG	1140
CAGCCGGAAA	AACCAAAACC	AGAGGTAA	CCGCAGCCGG	AAAAACCAAA	ACCAGAGGTT	1200
AAACCGCAGC	CGGAAAAACC	AAAACCAGAG	GTAAACCGC	AGCCGGAAAA	ACCAAAACCA	1260
GAGGTAAAC	CGCAGCCGGA	AAAACCAAAA	CCAGAGGTTA	AACCGCAACC	AGAAAAACCA	1320
AAACCAGAGG	TTAAACCGCA	ACCAGAAAAA	CCAAAACCCAG	ATAATAGCAA	GCCACAAGCA	1380
GATGATAAGA	AGCCATCAAC	TACAAATAAT	TTAAGCAAGG	ACAAGCAACC	TTCTAACCAA	1440
GCTTCAACAA	ACGAAAAAGC	AACAAATAAA	CCGAAGAAGT	CATTGCCATC	AACTGGATCT	1500
ATTTCAAATC	TAGCACTTGA	AATTGCAGGT	CTTCTTACCT	TGGCGGGGGC	AACCATTCTT	1560
GCTAAGAAA	GAATGAAATA	G	(SEQ ID NO: 5)			1581

FIGURE 5

MENIDMFKSN	HERRMYSIR	KFSVGVASVA	VASLFMGSVV	HATEKEGSTQ	50
AATSFNRGNG	SQAEQRGELD	LERDKAMKAV	SEYVGKMVRD	AYVKS DRKRH	100
KNTVALVNQL	GNIKNRYLNE	IVHSTSKSQL	QELMMKSQSE	VDEAVSKFEK	150
DSFSSSSSGS	STKPETPOPE	NPEHQKPTTP	SPDTKPSQP	EGKKPSVPDI	200
NQEKEKAKLA	VVTYMSKILD	DIQKHHLQKE	KHRQIVALIK	ELDELKKQAL	250
SEIDNVNTKV	EIENTVHKIF	ADMDAVVTKF	KKGLTQDTPK	EPGNKKPSAP	300
KPGMQPSPQP	EVKPQLEKPK	PEVKPQPEKP	KPEVKPQPEK	PKPEVKPQPE	350
KPKPEVKPQP	EKPKPEVKPQ	PEKPKPEVKP	QPEKPKPEVK	PQPEKPKPEV	400
KPQPEKPKPE	VKPQPEKPKP	EVKPQPEKPK	PEVKPQPEKP	KPEVKPQPEK	450
KPKDNSKPQA	DDKKPSTTNN	LSKDKQPSNQ	ASTNEKATNK	PKKSLPSTGS	500
ISNLALEIAG	LLTLGATIL	AKKRMK	(SEQ ID NO: 6)		526

FIGURE 6

ATGAAATTTA	GTAAAAAATA	TATAGCAGCT	GGATCAGCTG	TTATCGTATC	CTTGAGTCTA	60
TGTGCCTATG	CACTAAACCA	GCATCGTTCG	CAGGAAAATA	AGGACAATAA	TCGTGTCTCT	120
TATGTGGATG	GCAGCCAGTC	AAGTCAGAAA	AGTGAAAAC	TGACACCAGA	CCAGGTTAGC	180
CAGAAAGAAG	GAATTCAGGC	TGAGCAAATT	GTAATCAAAA	TTACAGATCA	GGGCTATGTA	240
ACGTACACAG	GTGACCACTA	TCATTACTAT	AATGGGAAAG	TTCCTTATGA	TGCCCTCTTT	300
AGTGAAGAAC	TCTTGATGAA	GGATCCAAAC	TATCAACTTA	AAGACGCTGA	TATTGTCAAT	360
GAAGTCAAGG	GTGGTTATAT	CATCAAGGTC	GATGGAAAAT	ATTATGTCTA	CCTGAAAGAT	420
GCAGCTCATG	CTGATAATGT	TCGAACTAAA	GATGAAATCA	ATCGTCAAAA	ACAAGAACAT	480
GTCAAAGATA	ATGAGAAGGT	TAACCTCTAAT	GTTGCTGTAG	CAAGGTCTCA	GGGACGATAT	540
ACGACAAATG	ATGGTTATGT	CTTTAATCCA	GCTGATATTA	TCGAAGATAC	GGGTAATGCT	600
TATATCGTTC	CTCATGGAGG	TCACTATCAC	TACATTCCCA	AAAGCGATTT	ATCTGCTAGT	660
GAATTAGCAG	CAGCTAAAGC	ACATCTGGCT	GGAAAAAATA	TGCAACCGAG	TCAGTTAAGC	720
TATTCTTCAA	CAGCTAGTGA	CAATAACACG	CAATCTGTAG	CAAAAGGATC	AACTAGCAAG	780
CCAGCAAATA	AATCTGAAAA	TCTCCAGAGT	CTTTTGAAGG	AACTCTATGA	TTCACCTAGC	840
GCCCAACGTT	ACAGTGAATC	AGATGGCCTG	GTCTTTGACC	CTGCTAAGAT	TATCAGTCGT	900
ACACCAAATG	GAGTTGCGAT	TCCGCATGGC	GACCATTACC	ACTTTATTCC	TTACAGCAAG	960
CTTTCTGCTT	TAGAAGAAAA	GATTGCCAGA	ATGGTGCCCTA	TCAGTGGAAC	TGGTTCTACA	1020
GTTTCTACAA	ATGCAAAACC	TAATGAAGTA	GTGTCTAGTC	TAGGCAGTCT	TTCAAGCAAT	1080
CCTTCTTCTT	TAACGACAAG	TAAGGAGCTC	TCTTCAGCAT	CTGATGGTTA	TATTTTAAAT	1140
CCAAAAGATA	TCGTTGAAGA	AACGGCTACA	GCTTATATTG	TAAGACATGG	TGATCATTTT	1200
CATTACATTC	CAAAATCAAA	TCAAATTGGG	CAACCGACTC	TTCCAAACAA	TAGTCTAGCA	1260
ACACCTTCTC	CATCTCTTCC	AATCAATCCA	GGAACCTCAC	ATGAGAAACA	TGAAGAAGAT	1320
GGATACGGAT	TTGATGCTAA	TCGTATTATC	GCTGAAGATG	AATCAGGTTT	TGTCATGAGT	1380
CACGGAGACC	ACAATCATT	TTTCTTCAAG	AAGGACTTGA	CAGAAGAGCA	AATTAAGGTT	1440
CGCAAAACA	TTTAG	(SEQ ID NO: 7)				1455

FIGURE 7

MKFSKKYIAA	GSAVIVLSL	CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	50
SENLTDPQVS	OKEGIQAEQI	VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	100
SEELLMKDPN	YQLKDADIVN	EVKGGYIIKV	DGKYVYVLKD	AAHADNVRTK	150
DEINRQKQEH	VKDNEKVNSN	VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	200
YIVPHGGHYH	YIPKSDLSAS	ELAAAKAHLA	GKNMQPSQLS	YSSTASDNNT	250
QSVAKGSTSK	PANKSENLOS	LLKELYDSPS	AQRYSESDGL	VFDPAKIISR	300
TPNGVAIPHG	DHYHFIPYSK	LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	350
VSSLGSLSSN	PSSLTTSKEL	SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	400
HYIPKSNQIG	QPTLPNNSLA	TPSPSLPINP	GTSHKHEED	GYGFDANRII	450
AEDESGFVMS	HGDHNHYFFK	KDLTEEQIKV	RKNI	(SEQ ID NO: 8)	484

FIGURE 8

ATGAAAGATT	TAGATAAAAA	AATCGAAGAA	AAAATTGCTG	GCATTATGAA	ACAATATGGT	60
GTCAAACGTG	AAAGTATTGT	CGTGAATAAA	GAAAAAAATG	CGATTATTTA	TCCGCATGGA	120
GATCACCATC	ATGCAGATCC	GATTGATGAA	CATAAACCGG	TTGGAATTGG	TCATTCTCAC	180
AGTAAGTATG	AACGTGTTAA	ACCCGAAGAA	GGAGTTGCTA	AAAAAGAAGG	GAATAAAGTT	240
TATACTGGAG	AAGAATTAAC	GAATGTTGTT	AATTTGTTAA	AAAATAGTAC	GTTTAATAAT	300
CAAACTTTTA	CTCTAGCCAA	TGGTCAAAAA	CGCGTTTCTT	TTAGTTTTC	GCCTGAATTG	360
GAGAAAAAAT	TAGGTATCAA	TATGCTAGTA	AAATTAATAA	CACCAGATGG	AAAAGTATTG	420
GAGAAAGTAT	CTGGTAAAGT	ATTTGGAGAA	GGAGTAGGGA	ATATTGCAAA	CTTTGAATTA	480
GATCAACCTT	ATTTACCAGG	ACAAACATTT	AAGTATACTA	TCGCTTCAAA	AGATTATCCA	540
GAAGTAAGTT	ATGATGGTAC	ATTTACAGTT	CCAACCTCTT	TAGCTTACAA	AATGGCCAGT	600
CAAACGATTT	TCTATCCTTT	CCATGCAGGG	GATACTTATT	TAAGAGTGAA	CCCTCAATTT	660
GCAGTGCCTA	AAGGAACTGA	TGCTTTAGTC	AGAGTGTTTG	ATGAATTTCA	TGGAAATGCT	720
TATTTAGAAA	ATAACTATAA	AGTTGGTGAA	ATCAAATTAC	CGATTCCGAA	ATTAAACCAA	780
GGAACAACCA	GAACGGCCGG	AAATAAAATT	CCTGTAACCT	TCATGGCAAA	TGCTTATTTG	840
GACAATCAAT	CGACTTATAT	TGTGGAAGTA	CCTATCTTGG	AAAAAGAAAA	TCAAACCTGAT	900
AAACCAAGTA	TTCTACCACA	ATTTAAAAGG	AATAAAGCAC	AAGAAAACTC	AAAACCTGAT	960
GAAAAGGTAG	AAGAACCAAA	GACTAGTGAG	AAGGTAGAAA	AAGAAAAACT	TTCTGAAACT	1020
GGAATAGTA	CTAGTAATTC	AACGTTAGAA	GAAGTTCCTA	CAGTGGATCC	TGTACAAGAA	1080
AAAGTAGCAA	AATTGCTGTA	AAGTTATGGG	ATGAAGCTAG	AAAATGTCTT	GTTTAATATG	1140
GACGGAACAA	TTGAATTATA	TTTACCATCA	GGAGAAGTCA	TTAAAAAGAA	TATGGCAGAT	1200
TTTACAGGAG	AAGCACCTCA	AGGAAATGGT	GAAAATAAAC	CATCTGAAAA	TGGAAAAGTA	1260
TCTACTGGAA	CAGTTGAGAA	CCAACCAACA	GAAAATAAAC	CAGCAGATTTC	TTTACCAGAG	1320
GCACCAAACG	AAAAACCTGT	AAAACCAGAA	AACTCAACGG	ATAATGGAAT	GTTGAATCCA	1380
GAAGGGAATG	TGGGGAGTGA	CCCTATGTTA	GATCCAGCAT	TAGAGGAAGC	TCCAGCAGTA	1440
GATCCTGTAC	AAGAAAAATT	AGAAAAATTT	ACAGCTAGTT	ACGGATTAGG	CTTAGATAGT	1500
GTTATATTCA	ATATGGATGG	AACGATTGAA	TTAAGATTGC	CAAGTGGAGA	AGTGATAAAA	1560
AAGAATTTAT	CTGATTTTCAT	AGCGTAA	(SEQ ID NO: 9)			1587

FIGURE 9

MKDLDKKIEE	KIAGIMKQYG	VKRESIVVNK	EKNAIIPPHG	DHHHADPIDE	50
HKPVGIGHSH	SNYELFKPEE	GVAKKEGNKV	YTGEELTNVV	NLLKNSTFNN	100
QNFTLANGQK	RVSFSFPPEL	EKKLGINMLV	KLITPDGKVL	EKVSGKVFGF	150
GVGNIANFEL	DQPYLPGQTF	KYTIASKDYP	EVSYDGTFTV	PTSLAYKMAS	200
QTIFYPPHAG	DTYLRVNPQF	AVPKGTDALV	RVFDEFHGNA	YLENNYKVGE	250
IKLPIPKLNQ	GTTRTAGNKI	PVTFMANAYL	DNQSTYIVEV	PILEKENQTD	300
KPSILPQFKR	NKAQENSKLD	EKVEEPTSE	KVEKEKLSET	GNSTSNSTLE	350
EVPTVDPVQE	KVAKFAESYG	MKLENVLFNM	DGTIELYLPS	GEVIKKNMAD	400
FTGEAPQGNG	ENKPSSENGV	STGTVENQPT	ENKPADSLPE	APNEKPVKPE	450
NSTDNGMLNP	EGNVGSDPML	DPALEEAPAV	DPVQEKLEKF	TASYGLGLDS	500
VIFNMDGTIE	LRLPSGEVIK	KNLSDFIA	(SEQ ID NO: 10)		528

FIGURE 10

BVH3 WU2	1	CAYALNQHRSQENKDNRRVSYVDGSSQSSQKSENLTDPQVSQKEGIAEQIVIKITDQGYV	60
BVH3 RX1	1	CAYALNQHRSQENKDNRRVSYVDGSSQSSQKSENLTDPQVSQKEGIAEQIVIKITDQGYV	60
BVH3 JNR7/87	1	CAYALNQHRSQENKDNRRVSYVDGSSQSSQKSENLTDPQVSQKEGIAEQIVIKITDQGYV	60
BVH3 SP64	1	CAYALNQHRSQENKDNRRVSYVDGSSQSSQKSENLTDPQVSQKEGIAEQIVIKITDQGYV	60
BVH3 P4241	1	CAYALNQHRSQENKDNRRVSYVDGSSQSSQKSENLTDPQVSQKEGIAEQIVIKITDQGYV	60
BVH3 A66	1	CAYALNQHRSQENKDNRRVSYVDGSSQSSQKSENLTDPQVSQKEGIAEQIVIKITDQGYV	60

BVH3 WU2	61	TSHGDHYHYNGKVPYDALFSEELMKDPNYQLKDADIVNEVKGGYIIKVDGKYVYVLKD	120
BVH3 RX1	61	TSHGDHYHYNGKVPYDALFSEELMKDPNYQLKDADIVNEVKGGYIIKVDGKYVYVLKD	120
BVH3 JNR7/87	61	TSHGDHYHYNGKVPYDALFSEELMKDPNYQLKDADIVNEVKGGYIIKVDGKYVYVLKD	120
BVH3 SP64	61	TSHGDHYHYNGKVPYDALFSEELMKDPNYQLKDADIVNEVKGGYIIKVDGKYVYVLKD	120
BVH3 P4241	61	TSHGDHYHYNGKVPYDALFSEELMKDPNYQLKDADIVNEVKGGYIIKVDGKYVYVLKD	120
BVH3 A66	61	TSHGDHYHYNGKVPYDALFSEELMKDPNYQLKDADIVNEVKGGYIIKVDGKYVYVLKD	120

BVH3 WU2	121	AAHADNVRTKDEINRQKQEHVKDNEKVNNSNVAVARSQGRYTTNDGYVFPADIIEDTGNA	180
BVH3 RX1	121	AAHADNVRTKDEINRQKQEHVKDNEKVNNSNVAVARSQGRYTTNDGYVFPADIIEDTGNA	180
BVH3 JNR7/87	121	AAHADNVRTKDEINRQKQEHVKDNEKVNNSNVAVARSQGRYTTNDGYVFPADIIEDTGNA	180
BVH3 SP64	121	AAHADNVRTKDEINRQKQEHVKDNEKVNNSNVAVARSQGRYTTNDGYVFPADIIEDTGNA	180
BVH3 P4241	121	AAHADNVRTKDEINRQKQEHVKDNEKVNNSNVAVARSQGRYTTNDGYVFPADIIEDTGNA	180
BVH3 A66	121	AAHADNVRTKDEINRQKQEHVKDNEKVNNSNVAVARSQGRYTTNDGYVFPADIIEDTGNA	180

BVH3 WU2	181	YIVPHRGHYHYIPKSDLSASELAAAKAHLAGKNMQPSQLSYSSSTASDNNTQSVAKGSTSK	240
BVH3 RX1	181	YIVPHGGHYHYIPKSDLSASELAAAKAHLAGKNMQPSQLSYSSSTASDNNTQSVAKGSTSK	240
BVH3 JNR7/87	181	YIVPHGGHYHYIPKSDLSASELAAAKAHLAGKNMQPSQLSYSSSTASDNNTQSVAKGSTSK	240
BVH3 SP64	181	YIVPHGGHYHYIPKSDLSASELAAAKAHLAGKNMQPSQLSYSSSTASDNNTQSVAKGSTSK	240
BVH3 P4241	181	YIVPHRGHYHYIPKSDLSASELAAAKAHLAGKNMQPSQLSYSSSTASDNNTQSVAKGSTSK	240
BVH3 A66	181	YIVPHRGHYHYIPKSDLSASELAAAKAHLAGKNMQPSQLSYSSSTASDNNTQSVAKGSTSK	240

BVH3 WU2	241	PANKSENLOSLKELYDSPAQRYSSESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPIYSK	300
BVH3 RX1	241	PANKSENLOSLKELYDSPAQRYSSESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPIYSK	300
BVH3 JNR7/87	241	PANKSENLOSLKELYDSPAQRYSSESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPIYSK	300
BVH3 SP64	241	PANKSENLOSLKELYDSPAQRYSSESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPIYSK	300
BVH3 P4241	241	PANKSENLOSLKELYDSPAQRYSSESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPIYSK	300
BVH3 A66	241	PANKSENLOSLKELYDSPAQRYSSESDGLVFDPAKIIISRTPNGVAIPHGDHYHFIPIYSK	300

BVH3 WU2	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSLGSLSSNPSSLTTSKELSSASDGYIFN	360
BVH3 RX1	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSLGSLSSNPSSLTTSKELSSASDGYIFN	360
BVH3 JNR7/87	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSLGSLSSNPSSLTTSKELSSASDGYIFN	360
BVH3 SP64	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSLGSLSSNPSSLTTSKELSSASDGYIFN	360
BVH3 P4241	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSLGSLSSNPSSLTTSKELSSASDGYIFN	360
BVH3 A66	301	LSALEEKIARMVPISGTGSTVSTNAKPNEVVSSLGSLSSNPSSLTTSKELSSASDGYIFN	360

BVH3 WU2	361	PKDIVEETATAYIVRHGDHPHYIPKSNQIGQPTLPNNSLATPSPSLPINPGTSHEKHEED	420
BVH3 RX1	361	PKDIVEETATAYIVRHGDHPHYIPKSNQIGQPTLPNNSLATPSPSLPINPGTSHEKHEED	420
BVH3 JNR7/87	361	PKDIVEETATAYIVRHGDHPHYIPKSNQIGQPTLPNNSLATPSPSLPINPGTSHEKHEED	420
BVH3 SP64	361	PKDIVEETATAYIVRHGDHPHYIPKSNQIGQPTLPNNSLATPSPSLPINPGTSHEKHEED	420
BVH3 P4241	361	PKDIVEETATAYIVRHGDHPHYIPKSNQIGQPTLPNNSLATPSPSLPINPGTSHEKHEED	420
BVH3 A66	361	PKDIVEETATAYIVRHGDHPHYIPKSNQIGQPTLPNNSLATPSPSLPINPGTSHEKHEED	420

BVH3 WU2	421	GYGFDANRIIAEDES GFVMSHGDNHNYFFKKDLTEEQIKAAQKHLEEVKTSHNGLDSLSS	480
BVH3 RX1	421	GYGFDANRIIAEDES GFVMSHGDNHNYFFKKDLTEEQIKAAQKHLEEVKTSHNGLDSLSS	480
BVH3 JNR7/87	421	GYGFDANRIIAEDES GFVMSHGDNHNYFFKKDLTEEQIKAAQKHLEEVKTSHNGLDSLSS	480
BVH3 SP64	421	GYGFDANRIIAEDES GFVMSHGDNHNYFFKKDLTEEQIKAAQKHLEEVKTSHNGLDSLSS	480
BVH3 P4241	421	GYGFDANRIIAEDES GFVMSHGDNHNYFFKKDLTEEQIKAAQKHLEEVKTSHNGLDSLSS	480
BVH3 A66	421	GYGFDANRIIAEDES GFVMSHGDNHNYFFKKDLTEEQIKAAQKHLEEVKTSHNGLDSLSS	480

BVH3 WU2	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
BVH3 RX1	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
BVH3 JNR7/87	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
BVH3 SP64	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
BVH3 P4241	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540
BVH3 A66	481	HEQDYPSNAKEMKDLKKIEEKIAGIMKQYGVKRESIVVNKEKNAIYPHGDHHDADPID	540

BVH3 WU2	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGKNVYTGEELTNVNNLLKNSTFNNQNFLLANGQ	600
BVH3 RX1	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGKNVYTGEELTNVNNLLKNSTFNNQNFLLANGQ	600
BVH3 JNR7/87	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGKNVYTGEELTNVNNLLKNSTFNNQNFLLANGQ	600
BVH3 SP64	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGKNVYTGEELTNVNNLLKNSTFNNQNFLLANGQ	600
BVH3 P4241	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGKNVYTGEELTNVNNLLKNSTFNNQNFLLANGQ	600
BVH3 A66	541	EHKPVGIGHSHSNYELFKPEEGVAKKEGKNVYTGEELTNVNNLLKNSTFNNQNFLLANGQ	600

BVH3 WU2	601	KRVSPFPPPELEKKLGINMLVKLITPDGKVLKESVSGKVFGEVGNIANFELDQPYLPQGT	660
BVH3 RX1	601	KRVSPFPPPELEKKLGINMLVKLITPDGKVLKESVSGKVFGEVGNIANFELDQPYLPQGT	660
BVH3 JNR7/87	601	KRVSPFPPPELEKKLGINMLVKLITPDGKVLKESVSGKVFGEVGNIANFELDQPYLPQGT	660
BVH3 SP64	601	KRVSPFPPPELEKKLGINMLVKLITPDGKVLKESVSGKVFGEVGNIANFELDQPYLPQGT	660
BVH3 P4241	601	KRVSPFPPPELEKKLGINMLVKLITPDGKVLKESVSGKVFGEVGNIANFELDQPYLPQGT	660
BVH3 A66	601	KRVSPFPPPELEKKLGINMLVKLITPDGKVLKESVSGKVFGEVGNIANFELDQPYLPQGT	660

BVH3 WU2	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
BVH3 RX1	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
BVH3 JNR7/87	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
BVH3 SP64	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
BVH3 P4241	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720
BVH3 A66	661	FKYTIASKDYPEVSYDGTFTVPTSLAYKMASQTIFFYPFHAGDTYLRVNPQFAVPKGTDAL	720

BVH3 WU2	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
BVH3 RX1	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
BVH3 JNR7/87	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
BVH3 SP64	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
BVH3 P4241	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780
BVH3 A66	721	VRVFDEFHGNAYLENNYKVGEIKLPIPKLNQGTTRTAGNKIPVTFMANAYLDNQSTYIVE	780

BVH3 WU2	781	VPILEKENQTDKPSILPQPKRKAQENSKFDEKVEEPTSEKVEKEKLSSETGNSTSNSTL	840
BVH3 RX1	781	VPILEKENQTDKPSILPQPKRKAQENSKFDEKVEEPTSEKVEKEKLSSETGNSTSNSTL	840
BVH3 JNR7/87	781	VPILEKENQTDKPSILPQPKRKAQENSKFDEKVEEPTSEKVEKEKLSSETGNSTSNSTL	840
BVH3 SP64	781	VPILEKENQTDKPSILPQPKRKAQENSKFDEKVEEPTSEKVEKEKLSSETGNSTSNSTL	840
BVH3 P4241	781	VPILEKENQTDKPSILPQPKRKAQENSKFDEKVEEPTSEKVEKEKLSSETGNSTSNSTL	840
BVH3 A66	781	VPILEKENQTDKPSILPQPKRKAQENSKFDEKVEEPTSEKVEKEKLSSETGNSTSNSTL	840

BVH3 WU2	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPDSGEVIKQNMADFTGEAPQGN	900
BVH3 RX1	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPDSGEVIKQNMADFTGEAPQGN	900
BVH3 JNR7/87	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPDSGEVIKQNMADFTGEAPQGN	900
BVH3 SP64	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPDSGEVIKQNMADFTGEAPQGN	900
BVH3 P4241	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPDSGEVIKQNMADFTGEAPQGN	900
BVH3 A66	841	EEVPTVDPVQEKVAKFAESYGMKLENVLFNMDGTIELYLPDSGEVIKQNMADFTGEAPQGN	900

BVH3 WU2	901	GENKPSENGKVSSTGTVENQPTENKPADSLPEAPNEKPVKPNSTNDGMLNPEGNVGSDPM	960
BVH3 RX1	901	GENKPSENGKVSSTGTVENQPTENKPADSLPEAPNEKPVKPNSTNDGMLNPEGNVGSDPM	960
BVH3 JNR7/87	901	GENKPSENGKVSSTGTVENQPTENKPADSLPEAPNEKPVKPNSTNDGMLNPEGNVGSDPM	960
BVH3 SP64	901	GENKPSENGKVSSTGTVENQPTENKPADSLPEAPNEKPVKPNSTNDGMLNPEGNVGSDPM	960
BVH3 P4241	901	GENKPSENGKVSSTGTVENQPTENKPADSLPEAPNEKPVKPNSTNDGMLNPEGNVGSDPM	960
BVH3 A66	901	GENKPSENGKVSSTGTVENQPTENKPADSLPEAPNEKPVKPNSTNDGMLNPEGNVGSDPM	960

BVH3 WU2	961	LDPALAEAPAVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKQNLSDLIA	1019
BVH3 RX1	961	LDPALAEAPAVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKQNLSDLIA	1019
BVH3 JNR7/87	961	LDPALAEAPAVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKQNLSDLIA	1019
BVH3 SP64	961	LDPALAEAPAVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKQNLSDLIA	1019
BVH3 P4241	961	LDPALAEAPAVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKQNLSDLIA	1019
BVH3 A66	961	LDPALAEAPAVDPVQEKLEKFTASYGLGLDSVIFNMDGTIELRLPSGEVIKQNLSDLIA	1019

FIGURE 11

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BVH11-2 SP64      1 CSYELGRHQAGQVKKESNRVSYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11-2 JNR7/87  1 CSYELGRHQAGQVKKESNRVSYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11-2 P4241    1 CSYELGRHQAGQDKKESNRVAYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11-2 A66      1 CSYELGRHQAGQDKKESNRVAYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11-2 WU2      1 CSYELGRHQAGQDKKESNRVAYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11-2 Rx1      1 CSYELGRHQAGQVKKESNRVSYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 P4241      1 CSYELGRHQAGQDKKESNRVAYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 WU2        1 CSYELGRHQAGQDKKESNRVAYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 A66        1 CSYELGRHQAGQDKKESNRVAYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 Rx1        1 CSYELGRHQAGQDKKESNRVAYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 JNR7/87    1 CSYELGRHQAGQDKKESNRVAYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 SP63       1 CSYELGRHQAGQVKKESNRVSYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 60
BVH11 SP64       1 CSYELGRHQAGQVKKESNRVSYIDGDAQGQKAENLTPDEVSKREGINAEQIVIKITDQGY 59
                  * . . . . .
BVH11-2 SP64      61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11-2 JNR7/87  61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11-2 P4241    61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11-2 A66      61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11-2 WU2      61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11-2 Rx1      61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11 P4241      61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11 WU2        61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11 A66        61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11 Rx1        61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11 JNR7/87    61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11 SP63       61 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 120
BVH11 SP64       60 VTSBGDHYHYNGKVPYDAI ISEELLMKDPNYQLKSDIVNEIKGGYVIKVDGKYYVYLYK 119
                  * . . . . .
BVH11-2 SP64      121 DAAHADNIRTKEEIKRQKQEHSHNHNSRA--DNAAAAAQAQGRYTDDGYIFNASDIE 177
BVH11-2 JNR7/87  121 DAAHADNIRTKEEIKRQKQEHSHNHGGSN--DQAVVAARAQGRYTDDGYIFNASDIE 178
BVH11-2 P4241    121 DAAHADNIRTKEEIKRQKQEHSHNHGGSN--DQAVVAARAQGRYTDDGYIFNASDIE 178
BVH11-2 A66      121 DAAHADNIRTKEEIKRQKQEHSHNHGGSN--DQAVVAARAQGRYTDDGYIFNASDIE 178
BVH11-2 WU2      121 DAAHADNIRTKEEIKRQKQEHSHNHGGSN--DQAVVAARAQGRYTDDGYIFNASDIE 178
BVH11-2 Rx1      121 DAAHADNIRTKEEIKRQKQEHSHNHNSRA--DNAAAAAQAQGRYTDDGYIFNASDIE 177
BVH11 P4241      121 DAAHADNIRTKEEIKRQKQEHSHNHGGSN--DQAVVAARAQGRYTDDGYIFNASDIE 178
BVH11 WU2        121 DAAHADNIRTKEEIKRQKQEHSHNHGGSN--DQAVVAARAQGRYTDDGYIFNASDIE 178
BVH11 A66        121 DAAHADNIRTKEEIKRQKQEHSHNHGGSN--DQAVVAARAQGRYTDDGYIFNASDIE 178
BVH11 Rx1        121 DAAHADNIRTKEEIKRQKQEHSHNHGGSN--DQAVVAARAQGRYTDDGYIFNASDIE 178
BVH11 JNR7/87    121 DAAHADNIRTKEEIKRQKQEHSHNHNSRA--DNAAAAAQAQGRYTDDGYIFNASDIE 177
BVH11 SP63       121 DAAHADNIRTKEEIKRQKQEHSHNHNSRA--DNAAAAAQAQGRYTDDGYIFNASDIE 177
BVH11 SP64       120 DAAHADNVRTKEEINRQKQEHSHNSREGGTSANDGAVAFARSQGRYTDDGYIFNASDIE 179
                  * . . . . .
BVH11-2 SP64      178 DTGDAYIVPHGDHYHYI PKNELSASELAAAEAYWNGKQGSRPSSSSSYNANPAQPRLSEN 237
BVH11-2 JNR7/87  179 DTGDAYIVPHGDHYHYI PKNELSASELAAAEAYWNGKQGSRPSSSSSYNANPAQPRLSEN 238
BVH11-2 P4241    179 DTGDAYIVPHGNHFHYI PKSDLSASELAAQAAYWNGKQGSRPSSSSSHNANPAQPRLSEN 238
BVH11-2 A66      179 DTGDAYIVPHGNHFHYI PKSDLSASELAAQAAYWNGKQGSRPSSSSSHNANPAQPRLSEN 238
BVH11-2 WU2      179 DTGDAYIVPRGNHFHYI PKSDLSASELAAQAAYWNGKQGSRPSSSSSHNANPAQPRLSEN 238
BVH11-2 Rx1      178 DTGDAYIVPHGDHYHYI PKSDLSASELAAQAAYWNGKQGSRPSSSSSHNANPAQPRLSEN 238
BVH11 P4241      179 DTGDAYIVPHGNHFHYI PKSDLSASELAAQAAYWNGKQGSRPSSSSSHNANPAQPRLSEN 238
BVH11 WU2        179 DTGDAYIVPHGNHFHYI PKSDLSASELAAQAAYWNGKQGSRPSSSSSHNANPAQPRLSEN 238
BVH11 A66        179 DTGDAYIVPHGNHFHYI PKSDLSASELAAQAAYWNGKQGSRPSSSSSHNANPAQPRLSEN 238
BVH11 Rx1        178 DTGDAYIVPHGNHFHYI PKSDLSASELAAQAAYWNGKQGSRPSSSSSHNANPAQPRLSEN 238
BVH11 JNR7/87    178 DTGDAYIVPHGDHYHYI PKNELSASELAAAEAYWNGKQGSRPSSSSSYNANPAQPRLSEN 237
BVH11 SP63       178 DTGDAYIVPHGNHFHYI PKSDLSASELAAQAAYWNGKQGSRPSSSSSHNANPAQPRLSEN 237
BVH11 SP64       180 DTGDAYIVPHGDHYHYI PKNELSASELAAAEAFLSGRANLSNLRTRYRRQNSDNTPTNWW 239
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BVH11-2 SP64      238 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 285
BVH11-2 JNR7/87  239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
BVH11-2 P4241    239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
BVH11-2 A66      239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
BVH11-2 WU2      239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
BVH11-2 Rx1      238 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 285
BVH11 P4241      239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
BVH11 WU2        239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
BVH11 A66        239 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 286
BVH11 Rx1        238 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 285
BVH11 JNR7/87    238 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 285
BVH11 SP63       238 HNLTVTPTYHQ-----QGENISSLLRELYAKPLSERHVESDGLIFDPAQITS 285
BVH11 SP64       240 PSVSNPGTTNTNTSNNSTNSQASQSNIDSLKQLYLPLSQRHVESDGLIFDPAQITS 299
      * * * * *
BVH11-2 SP64      286 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 345
BVH11-2 JNR7/87  287 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 346
BVH11-2 P4241    287 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 346
BVH11-2 A66      287 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 342
BVH11-2 WU2      287 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 342
BVH11-2 Rx1      286 RTANGVAVPHGDHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 345
BVH11 P4241      287 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 345
BVH11 WU2        287 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 342
BVH11 A66        287 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 342
BVH11 Rx1        286 RTANGVAVPHGDHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 342
BVH11 JNR7/87    286 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 345
BVH11 SP63       286 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 345
BVH11 SP64       300 RTARGVAVPHGNHYHFIPEYQMSLEEKRIARIIPLYRSNHWVPDSRPEQSPQSTPEPS 359
      * * * * *
BVH11-2 SP64      346 PSLQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 405
BVH11-2 JNR7/87  347 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 406
BVH11-2 P4241    343 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 402
BVH11-2 A66      343 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 402
BVH11-2 WU2      343 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 402
BVH11-2 Rx1      346 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 402
BVH11 P4241      343 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 405
BVH11 WU2        343 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 402
BVH11 A66        343 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 402
BVH11 Rx1        346 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 402
BVH11 JNR7/87    346 PSP-----QAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 399
BVH11 SP63       346 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSK 405
BVH11 SP64       360 PSPQAPAPNPQAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKNLSAETAAGIDSK 419
      * * * * *
BVH11-2 SP64      406 LAKQESLSHKLGAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 465
BVH11-2 JNR7/87  407 LAKQESLSHKLGAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 466
BVH11-2 P4241    403 LAKQESLSHKLGTAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 462
BVH11-2 A66      403 LAKQESLSHKLGTAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 462
BVH11-2 WU2      403 LAKQESLSHKLGTAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 462
BVH11-2 Rx1      406 LAKQESLSHKLGAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 465
BVH11 P4241      403 LAKQESLSHKLGTAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 462
BVH11 WU2        403 LAKQESLSHKLGTAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 462
BVH11 A66        403 LAKQESLSHKLGTAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 462
BVH11 Rx1        406 LAKQESLSHKLGAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 462
BVH11 JNR7/87    400 LAKQESLSHKLGAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 465
BVH11 SP63       406 LAKQESLSHKLGAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 459
BVH11 SP64       420 LAKQESLSHKLGAKKTDLPSSDREFYNKAYDLLARIHQDLDLNKGRQVDFEALDNLLERL 479
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BVH11-2 SP64      466 KDVSSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 525
BVH11-2 JNR7/87  467 KDVPSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 526
BVH11-2 P4241    463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11-2 A66      463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11-2 WU2      463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11-2 Rx1      466 KDVSSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 525
BVH11 P4241      463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11 WU2        463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11 A66        463 KDVSSDKVKLVVEDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 522
BVH11 Rx1        466 KDVSSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 525
BVH11 JNR7/87    460 KDVSSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 519
BVH11 SP63       466 EDVPSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 525
BVH11 SP64       480 KDVSSDKVKLVDDILAFAPIRHPERLGKPNQIITYTDDIEIQVAKLAGKYTTEDGYIFDP 539
    ** *****

BVH11-2 SP64      526 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 585
BVH11-2 JNR7/87  527 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 586
BVH11-2 P4241    523 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 582
BVH11-2 A66      523 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 582
BVH11-2 WU2      523 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 582
BVH11-2 Rx1      526 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 582
BVH11 P4241      523 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 582
BVH11 WU2        523 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 582
BVH11 A66        523 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 582
BVH11 Rx1        526 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 582
BVH11 JNR7/87    520 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 579
BVH11 SP63       526 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 585
BVH11 SP64       540 RDITSDEGDAYVTPHMTSHWIKKDSLSEAERAAQAAYAKEKGLTPPSTDHQDSGNTAK 599
    *****

BVH11-2 SP64      586 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 645
BVH11-2 JNR7/87  587 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 646
BVH11-2 P4241    583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11-2 A66      583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11-2 WU2      583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11-2 Rx1      586 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11 P4241      583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11 WU2        583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11 A66        583 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11 Rx1        586 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 642
BVH11 JNR7/87    580 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 639
BVH11 SP63       586 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 645
BVH11 SP64       600 GAEAIYNRVKAAKKVPLDRMPYNLQYTVVEVKGSLIIPHYDHYHNIKFEWFDEGLYEAPK 659
    *****

BVH11-2 SP64      646 GYSLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----ADQDSK 690
BVH11-2 JNR7/87  647 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----VDQDSK 691
BVH11-2 P4241    643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----ADQDSK 687
BVH11-2 A66      643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----ADQDSK 687
BVH11-2 WU2      643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----ADQDSK 687
BVH11-2 Rx1      646 GYSLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----ADQDSK 687
BVH11 P4241      643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----ADQDSK 687
BVH11 WU2        643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----ADQDSK 687
BVH11 A66        643 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----ADQDSK 687
BVH11 Rx1        646 GYSLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----ADQDSK 687
BVH11 JNR7/87    640 GYSLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----NGQ 687
BVH11 SP63       646 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----NGQ 681
BVH11 SP64       660 GYTLEDLLATVKYVVEHPNERPHSDNGFGNASDHVRKNK-----NGQ 701
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BVH11-2 SP64	691	PDEDKEHDEVSEPTHPESDEKENHAGLNPSADNLYKPSTDTETEEBAEDTTDEAEIPQV	750
BVH11-2 JNR7/87	692	PDEDKEHDEVSEPTHPESDEKENHAGLNPSADNLYKPSTDTETEEBAEDTTDEAEIPQV	751
BVH11-2 P4241	688	PDEDKGHDEVSEPTHPESDEKENHAGLNPSADNLYKPSTDTETEEBAEDTTDEAEIPQV	747
BVH11-2 A66	688	PDEDKGHDEVSEPTHPESDEKENHAGLNPSADNLYKPSTDTETEEBAEDTTDEAEIPQV	747
BVH11-2 WU2	688	PDEDKGHDEVSEPTHPESDEKENHAGLNPSADNLYKPSTDTETEEBAEDTTDEAEIPQV	747
BVH11-2 Rx1	706	PEEDKEHDEVSEPTHPESDEKENHAGLNPSADNLYKPSTDTETEEBAEDTTDEAEIPQV	765
BVH11 P4241	688	PDEDKGHDEVSEPTHPESDEKENHAGLNPSADNLYKPSTDTETEEBAEDTTDEAEIPQV	747
BVH11 WU2	688	PDEDKGHDEVSEPTHPESDEKENHAGLNPSADNLYKPSTDTETEEBAEDTTDEAEIPQV	747
BVH11 A66	688	PDEDKGHDEVSEPTHPESDEKENHAGLNPSADNLYKPSTDTETEEBAEDTTDEAEIPQV	747
BVH11 Rx1	688	ADTNQTEKPNEEKPQTEKPEEETPREKKPQSEKPSPKPTEEPREESPEESPEESEEPQV	747
BVH11 JNR7/87	682	ADTNQTEKPNEEKPQTEKPEEETPREKKPQSEKPSPKPTEEPREESPEESPEESEEPQV	741
BVH11 SP63	688	ADTNQTEKPSEKPPQTEKPEEETPREKKPQSEKPSPKPTEEPREESPEESPEESEEPQV	743
BVH11 SP64	702	ADTNQTEKPSEKPPQTEKPEEETPREKKPQSEKPSPKPTEEPREESPEESPEESEEPQV	757
		* * * * *	
BVH11-2 SP64	751	ENSVINAKIADAEALLEKVTDPSIRQNAMEITLGLKSSLLLGTKDNNTISAEVDSLLALL	810
BVH11-2 JNR7/87	752	ENSVINAKIADAEALLEKVTDPSIRQNAMEITLGLKSSLLLGTKDNNTISAEVDSLLALL	811
BVH11-2 P4241	748	EHSVINAKIADAEALLEKVTDPSIRQNAMEITLGLKSSLLLGTKDNNTISAEVDSLLALL	807
BVH11-2 A66	748	EHSVINAKIADAEALLEKVTDPSIRQNAMEITLGLKSSLLLGTKDNNTISAEVDSLLALL	807
BVH11-2 WU2	748	EHSVINAKIADAEALLEKVTDPSIRQNAMEITLGLKSSLLLGTKDNNTISAEVDSLLALL	807
BVH11-2 Rx1	766	EYSVINAKIADAEALLEKVTDSSIRQNAVETLGLKSSLLLGTKDNNTISAEVDSLLALL	825
BVH11 P4241	748	EHSVINAKIADAEALLEKVTDPSIRQNAMEITLGLKSSLLLGTKDNNTISAEVDSLLALL	807
BVH11 WU2	748	EHSVINAKIADAEALLEKVTDPSIRQNAMEITLGLKSSLLLGTKDNNTISAEVDSLLALL	807
BVH11 A66	748	EHSVINAKIADAEALLEKVTDPSIRQNAMEITLGLKSSLLLGTKDNNTISAEVDSLLALL	807
BVH11 Rx1	748	ETEKVKEKLREAEEDLLGKIQNPIIKSNAKETLTGLKNNLLFGTQDNNTIMAEAEKLLALL	807
BVH11 JNR7/87	742	ETEKVKEKLREAEEDLLGKIQNPIIKSNAKETLTGLKNNLLFGTQDNNTIMAEAEKLLALL	801
BVH11 SP63	744	ETEKVKEKLREAEEDLLGKIQNPIIKSNAKETLTGLKNNLLFGTQDNNTIMAEAEKLLALL	803
BVH11 SP64	758	ETEKVKEKLREAEEDLLGKIQNPIIKSNAKETLTGLKNNLLFGTQDNNTIMAEAEKLLALL	817
		* * * * *	
BVH11-2 SP64	811	KESQPAPIQ	819
BVH11-2 JNR7/87	812	KESQPAPIQ	820
BVH11-2 P4241	808	KKSQPAPIQ	816
BVH11-2 A66	808	KKSQPAPIQ	816
BVH11-2 WU2	808	KKSQPAPIQ	816
BVH11-2 Rx1	826	KESQPAPIQ	834
BVH11 P4241	808	KESK	811
BVH11 WU2	808	KESK	811
BVH11 A66	808	KESK	811
BVH11 Rx1	808	KESK	811
BVH11 JNR7/87	802	KESK	805
BVH11 SP63	804	KESK	807
BVH11 SP64	818	KESK	821
		* *	

FIGURE 12

BVH11-2 SP64	I 81% S 86%	BVH11 SP63	I 88% S 90%	BVH11 JNR.7/87	I 88% S 91%	BVH11-2 JNR.7/87	I 82% S 87%	BVH11 WU2	I 80% S 85%	BVH11-2 WU2	I 80% S 85%	BVH11 A66	I 80% S 85%	BVH11-2 A66	I 80% S 85%	BVH11 P4241	I 80% S 85%	BVH11-2 P4241	I 80% S 85%	BVH11 Rx-1	I 88% S 91%	BVH11-2 Rx-1	I 81% S 85%	BVH11 SP64
			I 87% S 90%		I 87% S 90%		I 98% S 98%		I 96% S 97%		I 96% S 97%		I 96% S 97%		I 96% S 97%		I 95% S 96%		I 96% S 97%		I 87% S 90%		I 94% S 95%	BVH11-2 SP64
			I 96% S 96%		I 88% S 91%		I 88% S 91%		I 87% S 90%		I 87% S 90%		I 87% S 90%		I 87% S 90%		I 88% S 91%		I 87% S 90%		I 97% S 97%		I 89% S 91%	BVH11 SP63
							I 87% S 91%		I 86% S 90%		I 86% S 90%		I 86% S 90%		I 86% S 90%		I 87% S 91%		I 86% S 90%		I 96% S 96%		I 88% S 90%	BVH11 JNR.7/87
							I 96% S 97%		I 97% S 98%		I 97% S 98%		I 97% S 98%		I 97% S 98%		I 96% S 97%		I 97% S 98%		I 87% S 90%		I 94% S 95%	BVH11-2 JNR.7/87
									I 98% S 98%		I 98% S 98%		I 98% S 98%		I 98% S 98%		I 99% S 99%		I 98% S 99%		I 87% S 91%		I 92% S 94%	BVH11 WU2
																	I 98% S 98%		I 99% S 99%		I 86% S 90%		I 93% S 95%	BVH11-2 WU2
																	I 99% S 99%		I 99% S 99%		I 87% S 91%		I 92% S 94%	BVH11 A66
																			I 99% S 99%		I 86% S 90%		I 93% S 95%	BVH11-2 A66
																					I 87% S 91%		I 92% S 94%	BVH11 P4241
																					I 86% S 90%		I 93% S 95%	BVH11-2 P4241
																							I 91% S 92%	BVH11 Rx-1

FIGURE 13

AAATCCTTGT	CGGGTAAGTT	CCGACCCGCA	CGAAAGGCGT	AATGATTTGG	GCACTGTCTC	60
AACGAGAGAC	TCGGTGAAAT	TTTAGTACCT	GTGAAGATGC	AGGTTACCCG	CGACAGGACG	120
GAAAGACCCC	ATGGAGCTTT	ACTGCAGTTT	GATATTGAGT	GTCTGTACCA	CATGTACAGG	180
ATAGGTAGGA	GTCTAAGAGA	TCGGGACGCC	AGTTTCGAAG	GAGACGCTGT	TGGGATACTA	240
CCCTTGTGTT	ATGGCCACTC	TAACCCAGAT	AGGTGATCCC	TATCGGAGAC	AGTGTCTGAC	300
GGGCAGTTTG	ACTGGGGCGG	TCGCCTCCTA	AAAGGTAACG	GAGGCGCCCA	AAGGTTCCCT	360
CAGAAATGGT	GGAAATCATT	CGCAGAGTGT	AAAGGTATAA	GGGAGCTTGA	CTGCGAGAGC	420
TACAACTCGA	GCAGGGACGA	AAGTCGGGCT	TAGTGATCCG	GTGGTTCCGT	ATGGAAGGGC	480
CATCGCTCAA	CGGATAAAAG	CTACCCTGGG	GATAACAGGC	TTATCTCCCC	CAAGAGTTCA	540
CATCGACGGG	GAGGTTTGGC	ACCTCGATGT	CGGCTCGTCG	CATCCTGGGG	CTGTAGTCGG	600
TCCCAAGGGT	TGGGCTGTTT	GCCCATTAA	GCGGCACGCG	AGCTGGGTTT	AGAACGTCGT	660
GAGACAGTTC	GGTCCCTATC	CGTCGCGGGC	GTAGGAAATT	TGAGAGGATC	TGCTCCTAGT	720
ACGAGAGGAC	CAGAGTGGAC	TTACCGCTGG	TGTACCAATT	GTCTTGCCAA	AGGCATCGCT	780
GGGTAGCTAT	GTAGGGAAGG	GATAAACGCT	GAAAGCATCT	AAGTGTGAAA	CCCACCTCAA	840
GATGAGATTT	CCCATGATTA	TATATCAGTA	AGAGCCCTGA	GAGATGATCA	GGTAGATAGG	900
TTAGAAGTGG	AAGTGTGGCG	ACACATGTAG	CGGACTAATA	CTAATAGCTC	GAGGACTTAT	960
CCAAAGTAA	CGGATAAAAG	CTACCCTGGG	GATAACAGGC	TTATCTCCCC	CAAGAGTTCA	1020
CGAACACAGA	AGTTAAGCCC	TAGAACGCCG	GAAGTAGTTG	GGGGTTGCCC	CCTGTGAGAT	1080
AGGGAAAGTCG	CTTAGCTCTA	GGGAGTTTAG	CTCAGCTGGG	AGAGCATCTG	CCTTACAAGC	1140
AGAGGGTCAG	CGGTTTCGATC	CCGTTAACTC	CCAAAGGTCC	CGTAGTGTAG	CGGTTATCAC	1200
GTCCGCCCTGT	CACGGCGAAG	ATCGCGGGTT	CGATTCCCGT	CGGGACCGTT	TAAGGTAACG	1260
CAAGTTATTT	TAGACTCGTT	AGCTCAGTTG	GTAGAGCAAT	TGACTTTTAA	TCAATGGGTC	1320
ACTGGTTTCA	GCCCAGTACG	GGTCATATAT	GCGGGTTTGG	CGGAATTCTA	ATCTCTTTGA	1380
AATCATCTTC	TCTCACTTTC	CAAACTCTA	TTACCTCTTA	TTATACCACA	TTTCAATCTT	1440
CAACTTCCCA	GTAATATAAG	CACCTCTGGC	GAAAGAAGTT	TCAATGTCCT	AAAGTAATAA	1500
GTGAATCCAA	TTCAGGAACT	CCAAGAACAA	AAGAAACATC	TGGTGTCA	AGTATTGGAT	1560
GGCACAGAGT	CACGTGGTAG	TCTGACCCTA	GCAGAAATTT	TAAATAGTAA	ACTATTTACT	1620
GGTTAATTAA	ATGGTTAAAT	AACCGGTTTA	GAAACTATT	TAATAAAGTA	AAAGAAGTTG	1680
AGAAAAAAT	TCATCATTTA	TTGAAATGAG	GGATTTATGA	AATTTAGTAA	AAAATATATA	1740
GCAGCTGGAT	CAGCTGTTAT	CGTATCCTTG	AGTCTATGTG	CCTATGCACT	AAACCAGCAT	1800
CGTTCGCAGG	AAAATAAGGA	CAATAATCGT	GTCTCTTATG	TGGATGGCAG	CCAGTCAAGT	1860
CAGAAAAGTG	AAAACCTTGAC	ACCAGACCAG	GTTAGCCAGA	AAGAAGGAAT	TCAGGCTGAG	1920
CAAATTGTAA	TCAAAATTAC	AGATCAGGGC	TATGTAACGT	CACACGGTGA	CCACTATCAT	1980
TACTATAATG	GGAAAGTTCC	TTATGATGCC	CTCTTTAGTG	AAGAACTCTT	GATGAAGGAT	2040
CCAAACTATC	AACTTAAAGA	CGCTGATATT	GTCAATGAAG	TCAAGGGTGG	TTATATCATC	2100
AAGGTCGATG	GAAAATATTA	TGTCTACCTG	AAAGATGCAG	CTCATGCTGA	TAATGTTCCA	2160
ACTAAAGATG	AAATCAATCG	TCAAAAACAA	GAACATGTCA	AAGATAATGA	GAAGGTTAAC	2220
TCTAATGTTG	CTGTAGCAAG	GTCTCAGGGA	CGATATACGA	CAAATGATGG	TTATGTCTTT	2280
AATCCAGCTG	ATATTATCGA	AGATACGGGT	AATGCTTATA	TCGTTCCCTA	TGGAGGTCAC	2340
TATCACTACA	TTCCCAAAAG	CGATTTATCT	GCTAGTGAAT	TAGCAGCAGC	TAAAGCACAT	2400
CTGGCTGGAA	AAAATATGCA	ACCGAGTCAG	TTAAGCTATT	CTTCAACAGC	TAGTGACAAT	2460
AACACGCAAT	CTGTAGCAAA	AGGATCAACT	AGCAAGCCAG	CAAATAAATC	TGAAAATCTC	2520
CAGAGTCTTT	TGAAGGAACT	CTATGATTCA	CCTAGCGCCC	AACGTTACAG	TGAATCAGAT	2580
GGCCTGGTCT	TTGACCCTGC	TAAGATTATC	AGTCGTACAC	CAAATGGAGT	TGCGATTCCG	2640
CATGGCGACC	ATTACCACTT	TATTCCTTAC	AGCAAGCTTT	CTGCTTTAGA	AGAAAAGATT	2700
GCCAGAATGG	TGCCTATCAG	TGGAAGTGGT	TCTCAGCTTT	CTACAAATGC	AAAACCTAAT	2760
GAAGTAGTGT	CTAGTCTAGG	CAGTCTTTCA	AGCAATCCTT	CTTCTTTAAC	GACAAGTAAG	2820
GAGCTCTCTT	CAGCATCTGA	TGGTTAATTT	TTAATCCAA	AAGATATCGT	TGAAGAAACG	2880
GCTACAGOTT	ATATTGTAAG	ACATGGTGAT	CATTTCCATT	ACATTCCAAA	ATCAAATCAA	2940
ATTGGGCAAC	CGACTCTTCC	AAACAATAGT	CTAGCAACAC	CTTCTCCATC	TCTTCCAATC	3000
AATCCAGGAA	CTTCACATGA	GAAACATGAA	GAAGATGGAT	ACGGATTGTA	TGCTAATCGT	3060
ATTATCGCTG	AAGATGAATC	AGGTTTGTG	ATGAGTCACG	GAGACCACAA	TCATTATTTT	3120
TTCAAGAAGG	ACTTGACAGA	AGAGCAAATT	AAGGCTGCGC	AAAAACATTT	AGAGGAAGTT	3180
AAAAGTAGTC	ATAATGGATT	AGATTCTTTG	TCATCTCATG	AACAGGATTA	TCCAGGTAAT	3240
GCCAAAGAAA	TGAAAGATTT	AGATAAAAAA	ATCGAAGAAA	AAATTGCTGG	CATTATGAAA	3300
						3360

CAATATGGTG	TCAAACGTGA	AAGTATTGTC	GTGAATAAAG	AAAAAAATGC	GATTATTTAT	3420
CCGCATGGAG	ATCACCATCA	TGCAGATCCG	ATTGATGAAC	ATAAACCGGT	TGGAATTGGT	3480
CATTCTCACA	GTAACATGA	ACTGTTTAAA	CCCGAAGAAG	GAGTTGCTAA	AAAAGAAGGG	3540
AATAAAGTTT	ATACTGGAGA	AGAATTAAACG	AATGTTGTTA	ATTGTTAAA	AAATAGTACG	3600
TTTAATAATC	AAAACTTTAC	TCTAGCCAAT	GGTCAAAAAC	GCGTTTCTTT	TAGTTTTCCG	3660
CCTGAATTGG	AGAAAAAATT	AGGTATCAAT	ATGCTAGTAA	AATTAATAAC	ACCAGATGGA	3720
AAAGTATTGG	AGAAAGTATC	TGGTAAAGTA	TTTGGAGAAG	GAGTAGGGAA	TATTGCAAAAC	3780
TTTGAATTAG	ATCAACCTTA	TTTACCAGGA	CAAACATTTA	AGTATACTAT	CGCTTCAAAA	3840
GATTATCCAG	AAGTAAGTTA	TGATGGTACA	TTTACAGTTC	CAACCTCTTT	AGCTTACAAA	3900
ATGGCCAGTC	AAACGATTTT	CTATCCTTTC	CATGCAGGGG	ATACTTATTT	AAGAGTGAAC	3960
CCTCAATTTG	CAGTGCCTAA	AGGAACTGAT	GCTTTAGTCA	GAGTGTTTGA	TGAATTTTCAT	4020
GGAAATGCTT	ATTTAGAAAA	TAACATAAAA	GTTGGTGAAA	TCAAATTACC	GATTCCGAAA	4080
TTAAACCAAG	GAACAACCAG	AACGGCCGGA	AATAAAAATTC	CTGTAACCTT	CATGGCAAAT	4140
GCTTATTTGG	ACAATCAATC	GACTTATATT	GTGGAAGTAC	CTATCTTGGA	AAAAGAAAAT	4200
CAAACGATA	AACCAAGTAT	TCTACCACAA	TTTAAAAGGA	ATAAAGCACA	AGAAAACTCA	4260
AAACTTGATG	AAAAGGTAGA	AGAACCAAAG	ACTAGTGAGA	AGGTAGAAAA	AGAAAAACTT	4320
TCTGAACTG	GGAATAGTAC	TAGTAATTCA	ACGTTAGAAG	AAGTTCCTAC	AGTGGATCCT	4380
GTACAAGAAA	AAGTAGCAAA	ATTTGCTGAA	AGTTATGGGA	TGAAGCTAGA	AAATGTCTTG	4440
TTTAATATGG	ACGGAACAAT	TGAATTATAT	TTACCATCAG	GAGAAGTCAT	TAAAAAGAAT	4500
ATGGCAGATT	TTACAGGAGA	AGCACCTCAA	GGAAATGGTG	AAAATAAACC	ATCTGAAAAAT	4560
GGAAAAGTAT	CTACTGGAAC	AGTTGAGAAC	CAACCAACAG	AAAATAAACC	AGCAGATTCT	4620
TTACCAGAGG	CACCAAACGA	AAAACCTGTA	AAACCAGAAA	ACTCAACGGA	TAATGGAATG	4680
TTGAATCCAG	AAGGGAATGT	GGGGAGTGAC	CCTATGTTAG	ATCCAGCATT	AGAGGAAGCT	4740
CCAGCAGTAG	ATCCTGTACA	AGAAAAATTA	GAAAAATTTA	CAGCTAGTTA	CGGATTAGGC	4800
TTAGATAGTG	TTATATTCAA	TATGGATGGA	ACGATTGAAT	TAAGATTGCC	AAGTGGAGAA	4860
GTGATAAAAA	AGAATTTATC	TGATTTTCATA	GCGTAAGGAA	TAGCAGTAGA	AAAAGTCTGA	4920
ATCAAAAAATG	AAGTTCTCTC	AAAAGTTAGA	AATAAACTC	TGACTTTGGG	AGAATTTTCAT	4980
TTTATTATTA	ATATATAAAA	TTTCTTGACA	TACAACTTAA	AAAGAGGTGG	AATATTTACT	5040
AGTTAATT	(SEQ ID NO : 11)					5048

FIGURE 14

CAGAGATCTT	AGTGAATCAA	ATATACTTAA	GAAAAGAGGA	AAGAATGAAA	ATCAATAAAA	60
AATATCTAGC	TGGGTCAGTA	GCTACACTTG	TTTAAAGTGT	CTGTGCTTAT	GAAGTAGGTT	120
TGCATCAAGC	TCAAACGTGA	AAAGAAAATA	ATCGTGTTC	CTATATAGAT	GGAAAACAAG	180
CGACGCAAAA	AACGGAGAAT	TTGACTCCTG	ATGAGGTTAG	CAAGCGTGAA	GGAAATCAACG	240
CCGAACAAAT	CGTCATCAAG	ATTACGGATC	AAGGTTATGT	GACCTCTCAT	GGAGACCATT	300
ATCATTACTA	TAATGGCAAG	GTCCCTTATG	ATGCCATCAT	CAGTGAAGAG	CTCCTCATGA	360
AAGATCCGAA	TTATCAGTTG	AAGGATTGAG	ACATTGTCAA	TGAAATCAAG	GGTGGTTATG	420
TCATTAAGGT	AAACGGTAAA	TACTATGTTT	ACCTTAAGGA	TGCAGCTCAT	GCGGATAATG	480
TCCGTACAAA	AGAAGAAATC	AATCGGCAAA	AACAAGAACA	TAGTCAGCAT	CGTGAAGGAG	540
GGACTTCAGC	AAACGATGGT	GCGGTAGCCT	TTGCACGTTT	ACAGGGACGC	TACACCACAG	600
ATGATGGTTA	TATCTTCAAT	GCATCTGATA	TCATCGAAGA	TACGGGCGAT	GCCTATATCG	660
TTCTCATGCG	AGATCATTAC	CATTACATTC	CTAAGAATGA	GTTATCAGCT	AGCGAGTTGG	720
CTGCTGCAGA	AGCCTTCCTA	TCTGGTCGGG	AAAATCTGTC	AAATTTAAGA	ACCTATCGCC	780
GACAAAATAG	CGATAACACT	CCAAGAACAA	ACTGGGTACC	TTCTGTAAGC	AATCCAGGAA	840
CTACAAATAC	TAACACAAGC	AACAACAGCA	ACACTAACAG	TCAAGCAAGT	CAAAGTAATG	900
ACATTGATAG	TCTCTTGAAA	CAGCTCTACA	AAGTGCCTTT	GAGTCAACGC	CATGTAGAAT	960
CTGATGGCCT	TATTTTCGAC	CCAGCGCAAA	TCACAAGTCG	AACCGCCAGA	GGTGTAGCTG	1020
TCCCTCATGG	TAACCATTAC	CACTTTATCC	CTTATGAACA	AATGTCTGAA	TTGGAAAAAC	1080
GAATTGCTCG	TATTATTCCC	CTTCGTTATC	GTTCAAACCA	TTGGGTACCA	GATTCAAGAC	1140
CAGAAGAACC	AAGTCCACAA	CCGACTCCAG	AACCTAGTCC	AAGTCCGCAA	CCTGCACCAA	1200
ATCCTCAACC	AGCTCCAAGC	AATCCAATTG	ATGAGAAATT	GGTCAAAGAA	GCTGTTCCGAA	1260
AAGTAGGCGA	TGGTTATGTC	TTTGAGGAGA	ATGGAGTTTC	TCGTTATATC	CCAGCCAAGA	1320
ATCTTTCAGC	AGAAACAGCA	GCAGGCATTG	ATAGCAAAC	GGCCAAGCAG	GAAAGTTTAT	1380
CTCATAAGCT	AGGAGCTAAG	AAAACGTACC	TCCCATCTAG	TGATCGAGAA	TTTTACAATA	1440
AGGCTTATGA	CTTACTAGCA	AGAATTCACC	AAGATTTACT	TGATAATAAA	GGTCGACAAG	1500
TTGATTTTGA	GGCTTTGGAT	AACCTGTTGG	AACGACTCAA	GGATGTCTCA	AGTGATAAAG	1560
TCAAGTTAGT	GGATGATATT	CTTGCCCTCT	TAGCTCCGAT	TCGTCAATCA	GAACGTTTAG	1620
GAAAACCAAA	TGCGCAAATT	ACCTACACTG	ATGATGAGAT	TCAAGTAGCC	AAGTTGGCAG	1680
GCAAGTACAC	AACAGAAGAC	GGTTATATCT	TTGATCCTCG	TGATATAACC	AGTGATGAGG	1740
GGGATGCCTA	TGTAACCTCA	CATATGACCC	ATAGCCACTG	GATTAAAAAA	GATAGTTTGT	1800
CTGAAGCTGA	GAGAGCGGCA	GCCCAGGCTT	ATGCTAAAGA	GAAAGGTTTG	ACCCCTCCTT	1860
CGACAGACCA	TCAGGATTCA	GGAAATACTG	AGGCAAAAGG	AGCAGAAGCT	ATCTACAACC	1920
GCGTGAAAGC	AGCTAAGAAG	GTGCCACTTG	ATCGTATGCC	TTACAATCTT	CAATATACTG	1980
TAGAAGTCAA	AAACGGTAGT	TTAATCATA	CTCATTATGA	CCATTACCAT	AACATCAAAT	2040
TTGAGTGGTT	TGACGAAGGC	CTTTATGAGG	CACCTAAGGG	GTATACTCTT	GAGGATCTTT	2100
TGGCGACTGT	CAAGTACTAT	GTCGAACATC	CAAACGAACG	TCCGCATTCA	GATAATGGTT	2160
TTGGTAACGC	TAGCGACCAT	GTTCAAAGAA	ACAAAAATGG	TCAAGCTGAT	ACCAATCAAA	2220
CGGAAAAACC	AAGCGAGGAG	AAACCTCAGA	CAGAAAAACC	TGAGGAAGAA	ACCCCTCGAG	2280
AAGAGAAACC	ACAAAGCGAG	AAACCAGAGT	CTCCAAAACC	AACAGAGGAA	CCAGAAGAAG	2340
AATCACCAGA	GGAATCAGAA	GAACCTCAGG	TCGAGACTGA	AAAGGTTGAA	GAAAAACTGA	2400
GAGAGGCTGA	AGATTTACTT	GGAAAAATCC	AGGATCCAAT	TATCAAGTCC	AATGCCAAG	2460
AGACTCTCAC	AGGATTAAAA	AATAATTTAC	TATTTGGCAC	CCAGGACAAC	AATACTATTA	2520
TGGCAGAAGC	TGAAAAACTA	TTGGCTTTAT	TAAAGGAGAG	TAAGTAAAGG	TAGCAGCATT	2580
TTCTAACTCC	TAAAAACAGG	ATAGGAGAAC	GGGAAAACGA	AAAATGAGAG	CAGAATGTGA	2640
GTTCTAG	(SED ID NO : 12)					2647

FIGURE 15

GGGTCTTAAA	ACTCTGAATC	CTTTAGAGGC	AGACCCACAA	AATGACAAGA	CCTATTTAGA	60
AAATCTGGAA	GAAAAATATGA	GTGTTCTAGC	AGAAGAATTA	AAGTGAGGAA	AGAATGAAAA	120
TCAATAAAAA	ATATCTAGCA	GGTTCAGTGG	CAGTCCTTGC	CCTAAGTGTT	TGTTCCCTATG	180
AACCTGGTCG	TCACCAAGCT	GGTCAGGTTA	AGAAAGAGTC	TAATCGAGTT	TCTTATATAG	240
ATGGTGATCA	GGCTGGTCAA	AAGGCAGAAA	ATTTGACACC	AGATGAAGTC	AGTAAGAGAG	300
AGGGGATCAA	CGCCGAACAA	ATTGTTATCA	AGATTACGGA	TCAAGGTTAT	GTGACCTCTC	360
ATGGAGACCA	TTATCATTAC	TATAATGGCA	AGGTTCTTTA	TGATGCCATC	ATCAGTGAAG	420
AACCTTCTCAT	GAAAGATCCG	AATTATCAGT	TGAAGGATTC	AGACATTGTC	AATGAAATCA	480
AGGGTGGCTA	TGTGATTAAG	GTAGACGGAA	AATACTATGT	TTACCTTAAA	GATGCGGCCC	540
ATGCGGACAA	TATTCGGACA	AAAGAAGAGA	TTAAACGTCA	GAAGCAGGAA	CACAGTCATA	600
ATCATAACTC	AAGAGCAGAT	AATGCTGTTG	CTGCAGCCAG	AGCCCAAGGA	CGTTATACAA	660
CGGATGATGG	GTATATCTTC	AATGCATCTG	ATATCATTGA	GGACACGGGT	GATGCTTATA	720
TCGTTTCCTCA	CGGCGACCAT	TACCATTACA	TTCTTAAGAA	TGAGTTATCA	GCTAGCGAGT	780
TAGCTGCTGC	AGAAGCCTAT	TGGAATGGGA	AGCAGGGATC	TCGTCTTCT	TCAAGTTCTA	840
GTTATAATGC	AAATCCAGTT	CAACCAAGAT	TGTCAGAGAA	CCACAATCTG	ACTGTCACCTC	900
CAACTTATCA	TCAAAATCAA	GGGGAACAA	TTTCAAGCCT	TTTACGTGAA	TTGTATGCTA	960
AACCTTATC	AGAACGCCAT	GTAGAATCTG	ATGGCCTTAT	TTTCGACCCA	GCGCAAATCA	1020
CAAGTCGAAC	CGCCAGAGGT	GTAGCTGTCC	CTCATGGTAA	CCATTACCAC	TTTATCCCTT	1080
ATGAACAAAT	GTCTGAATTG	GAAAAACGAA	TTGCTCGTAT	TATTCCTT	CGTTATCGTT	1140
CAAACCATTTG	GGTACCAGAT	TCAAGACCGAG	AACAACCAAG	TCCACAATCG	ACTCCGGAAC	1200
CTAGTCCAAG	TCTGCAACCT	GCACCAATC	CTCAACCAGC	TCCAAGCAAT	CCAATTGATG	1260
AGAAATTGGT	CAAAGAAGCT	GTTTCGAAAAG	TAGGCGATGG	TTATGTCTTT	GAGGAGAATG	1320
GAGTTTCTCG	TTATATCCCA	GCCAAGGATC	TTTCAGCAGA	AACAGCAGCA	GGCATTGATA	1380
GCAAACTGGC	CAAGCAGGAA	AGTTTATCTC	ATAAGCTAGG	AGCTAAGAAA	ACTGACCTCC	1440
CATCTAGTGA	TCGAGAATTT	TACAATAAGG	CTTATGACTT	ACTAGCAAGA	ATTACCAAG	1500
ATTTACTTGA	TAATAAAGGT	CGACAAGTTG	ATTTTGAGGT	TTTGATAAC	CTGTTGGAAC	1560
GACTCAAGGA	TGTCTCAAGT	GATAAAGTCA	AGTTAGTGGA	TGATATTCTT	GCCTTCTTAG	1620
CTCCGATTTCG	TCATCCAGAA	CGTTTAGGAA	AACCAATGC	GCAAATTACC	TACACTGATG	1680
ATGAGATTCA	AGTAGCCAAG	TTGGCAGGCA	AGTACACAAC	AGAAGACGGT	TATATCTTTG	1740
ATCCTCGTGA	TATAACCAGT	GATGAGGGGG	ATGCCTATGT	AACTCCACAT	ATGACCCATA	1800
GCCACTGGAT	TAAAAAAGAT	AGTTTGTCTG	AAGCTGAGAG	AGCGGCAGCC	CAGGCTTATG	1860
CTAAAGAGAA	AGGTTTGACC	CCTCCTTCGA	CAGACCACCA	GGATTTCAGGA	AATACTGAGG	1920
CAAAGGAGC	AGAAGCTATC	TACAACCGCG	TGAAAGCAGC	TAAGAAGGTG	CCACTTGATC	1980
GTATGCCTTA	CAATCTTCAA	TATACTGTAG	AAGTCAAAAA	CGGTAGTTTA	ATCATACCTC	2040
ATTATGACCA	TTACCATAAC	ATCAAATTTG	AGTGGTTTGA	CGAAGGCCTT	TATGAGGCAC	2100
CTAAGGGGTA	TAGTCTTGAG	GATCTTTTGG	CGACTGTCAA	GTACTATGTC	GAACATCCAA	2160
ACGAACGTCC	GCATTCAGAT	AATGGTTTTG	GTAACGCTAG	TGACCATGTT	CGTAAAAATA	2220
AGGCAGACCA	AGATAGTAAA	CCTGATGAAG	ATAAGGAACA	TGATGAAGTA	AGTGAGCCAA	2280
CTCACCTTGA	ATCTGATGAA	AAAGAGAATC	ACGCTGGTTT	AAATCCTTCA	GCAGATAATC	2340
TTTATAAACC	AAGCACTGAT	ACGGAAGAGA	CAGAGGAAGA	AGCTGAAGAT	ACCACAGATG	2400
AGGCTGAAAT	TCCTCAAGTA	GAGAATTCTG	TTATTAACGC	TAAGATAGCA	GATGCGGAGG	2460
CCTTGCTAGA	AAAAGTAACA	GATCCTAGTA	TTAGACAAAA	TGCTATGGAG	ACATTGACTG	2520
GTCTAAAAAG	TAGTCTTCTT	CTCGGAACGA	AAGATAATAA	CACTATTTCA	GCAGAAGTAG	2580
ATAGTCTCTT	GGCTTTGTTA	AAAGAAAGTC	AACCGGCTCC	TATACAGTAG	TAAAAATGAA	2639

(SEQ ID NO : 13)

FIGURE 16

MKINKKYL	AG	SVAVLALSVC	SYELGRHQAG	QVKKESNRVS	YIDGDAQGQK	50
AENLTPDEV	S	KREGINAEQI	VIKITDQGYV	TSHGDHYHY	NGKVPYDAII	100
SEELLMKDP	N	YQLKDSDIVN	EIKGGYVIKV	DGKYVYVLKD	AAHADNIRTK	150
EEIKRQKQEH		SHNHNSRADN	AVAAAAAQGR	YTDDGYIFN	ASDIIEDTGD	200
AYIVPHGDHY		HYIPKNELSA	SELAAAEAYW	NGKQGSRPSS	SSSYNANPVQ	250
PRLSENHNLT		VTPTYHONQG	ENISSLLREL	YAKPLSERHV	ESDGLIFDPA	300
QITSRTARGV		AVPHGNHYHF	IPYEQMSELE	KRIARIIPLR	YRSNHWVPDS	350
RPEQSPQST		PEPSPSLQPA	PNPQPAPSNP	IDEKLVKEAV	RKVGDDGYVFE	400
ENGVSRYIPA		KDLSAETAAG	IDSKLAKQES	LSHKLGAUKT	DLPSSDREFY	450
NKAYDLLARI		HQDLLDNKGR	QVDFEVLN	LERLKDVS	KVKLVDDILA	500
FLAPIRHPER		LGKPNAQITY	TDDEIQVAKL	AGKYTTEDGY	IFDPRDITS	550
EGDAYVTPHM		THSHWIKKDS	LSEAERAAQ	AYAKEKGLTP	PSTDHQDSGN	600
TEAKGAELIY		NRVKAACKVP	LDRMPYNLQY	TVEVKNGSLI	IPHYDHYHNI	650
KFEWFDEGLY		EAPKGYSLED	LLATVKYYVE	HPNERPHSDN	GFGNASDHVR	700
KNKADQDSKP		DEDKEHDEVS	EPHPESDEK	ENHAGLNPSA	DNLYKPSTDT	750
EETEEEAEDT		TDEAEIPQVE	NSVINAKIAD	AEALLEKVTD	PSIRQNAMET	800
LTGLKSSLLL		GTKDNNTISA	EVDSLLALLK	ESQPAPIQ		838

(SEQ ID NO : 14)

FIGURE 17

TGTGCCTATG	CACTAAACCA	GCATCGTTCG	CAGGAAAATA	AGGACAATAA	TCGTGTCTCT	60
TATGTGGATG	GCAGCCAGTC	AAGTCAGAAA	AGTGAAAACT	TGACACCAGA	CCAGGTTAGC	120
CAGAAAGAAG	GAATTCAGGC	TGAGCAAATT	GTAAATCAAAA	TTACAGATCA	GGGCTATGTA	180
ACGTCACACG	GTGATCACTA	TCATTACTAT	AATGGGAAAG	TTCCTTATGA	TGCCCTCTTT	240
AGTGAAGAAC	TCTTGATGAA	GGATCCAAAC	TATCAACTTA	AAGACGCTGA	TATTGTCAAT	300
GAAGTCAAGG	GTGGTTATAT	CATCAAGGTC	GATGGAAAAAT	ATTATGTCTA	CCTGAAAGAT	360
GCAGCTCATG	CTGATAATGT	TCGAACTAAA	GATGAAATCA	ATCGTCAAAA	ACAAGAACAT	420
GTCAAAGATA	ATGAGAAGGT	TAACCTCTAAT	GTTGCTGTAG	CAAGGTCTCA	GGGACGATAT	480
ACGACAAATG	ATGGTTATGT	CTTTAATCCA	GCTGATATTA	TCGAAGATAC	GGGTAATGCT	540
TATATCGTTC	CTCATGGAGG	TCACCTATCAC	TACATTCCCA	AAAGCGATT	ATCTGCTAGT	600
GAATTAGCAG	CAGCTAAAGC	ACATCTGGCT	GGAAAAATA	TGCAACCGAG	TCAGTTAAGC	660
TATTCTTCAA	CACCTTCTCC	ATCTCTTCCA	ATCAATCCAG	GAACCTCACA	TGAGAAACAT	720
GAAGAAGATG	GATACGGATT	TGATGCTAAT	CGTATTATCG	CTGAAGATGA	ATCAGGTTTT	780
GTCATGAGTC	ACGGAGACCA	CAATCATTAT	TTCTTCAAGA	AGGACTTGAC	AGAAGAGCAA	840
ATTAAGGCTG	CGCAAAAACA	TTTAGAGGAA	GTTAAAACTA	GTCATAATGG	ATTAGATTCT	900
TTGTCATCTC	ATGAACAGGA	TTATCCAAGT	AATGCCAAAG	AAATGAAAGA	TTTAGATAAA	960
AAAATCGAAG	AAAAAATTGC	TGGCATTATG	AAACAATATG	GTGTCAAACG	TGAAAGTATT	1020
GTCGTGAATA	AAGAAAAAAA	TGCGATTATT	TATCCGCATG	GAGATCACCA	TCATGCAGAT	1080
CCGATTGATG	AACATAAACC	GGTTGGAATT	GGTCATTCTC	ACAGTAACTA	TGAACCTGTT	1140
AAACCCGAAG	AAGGAGTTGC	TAAAAAAGAA	GGGAATAAAG	TTTATACTGG	AGAAGAATTA	1200
ACGAATGTTG	TTAATTTGTT	AAAAAATAGT	ACGTTTAATA	ATCAAAACTT	TACTCTAGCC	1260
AATGGTCAAA	AACGCGTTTC	TTTtagTTTT	CCGCCTGAAT	TGGAGAAAAA	ATTAGGTATC	1320
AATATGCTAG	TAAAATTAAT	AACACCAGAT	GGAAAAGTAT	TGGAGAAAGT	ATCTGGTAAA	1380
GTATTTGGAG	AAGGAGTAGG	GAATATTGCA	AACTTTGAAT	TAGATCAACC	TTATTTACCA	1440
GGACAAACAT	TTAAGTATAC	TATCGCTTCA	AAAGATTATC	CAGAAGTAAG	TTATGATGGT	1500
ACATTTACAG	TTCCAACCTC	TTTAGCTTAC	AAAATGGCCA	GTCAAACGAT	TTTCTATCCT	1560
TTCCATGCAG	GGGATACTTA	TTTAAGAGTG	AACCTTCAAT	TTGCAGTGCC	TAAAGGAAC	1620
GATGCTTTAG	TCAGAGTGTT	TGATGAATTT	CATGGAAATG	CTTATTTAGA	AAATAACTAT	1680
AAAGTTGGTG	AAATCAAAAT	ACCGATTCCG	AAATTAACC	AAGGAACAAC	CAGAACGGCC	1740
GGAAATAAAA	TTCTGTAAAC	CTTCATGGCA	AATGCTTATT	TGGACAATCA	ATCGACTTAT	1800
ATTGTGGAAG	TACCTATCTT	GGAAAAAGAA	AATCAAACTG	ATAAACCAAG	TATTCTACCA	1860
CAATTTAAAA	GGAATAAAGC	ACAAGAAAAC	TCAAACTTG	ATGAAAAGGT	AGAAGAACCA	1920
AAGACTAGTG	AGAAGGTAGA	AAAAGAAAAA	CTTCTGAAA	CTGGGAATAG	TACTAGTAAT	1980
TCAACGTTAG	AAGAAGTTCC	TACAGTGGAT	CCTGTACAAG	AAAAAGTAGC	AAAATTTGCT	2040
GAAAGTTATG	GGATGAAGCT	AGAAAATGTC	TTGTTTAATA	TGGACGGAAC	AATTGAATTA	2100
TATTTACCAT	CGGGAGAAGT	CATTAAAAAG	AATATGGCAG	ATTTTACAGG	AGAAGCACCT	2160
CAAGGAAATG	GTGAAAATAA	ACCATCTGAA	AATGGAAAAG	TATCTACTGG	AACAGTTGAG	2220
AACCAACCAA	CAGAAAATAA	ACCAGCAGAT	TCTTTACCA	AGGCACCAAA	CGAAAAACCT	2280
GTAACCAACG	AAAACCTAAC	GGATAATGGA	ATGTTGAATC	CAGAAGGGAA	TGTGGGGAGT	2340
GACCTTATGT	TAGATTTCAGC	ATTAGAGGAA	GCTCCAGCAG	TAGATCCTGT	ACAAGAAAAA	2400
TTAGAAAAAT	TTACAGCTAG	TTACGGATTA	GGCTTAGATA	GTGTTATATT	CAATATGGAT	2460
GGAACGATTG	AATTAAGATT	GCCAAGTGGA	GAAGTGATAA	AAAAGAATTT	ATTGATCTCA	2520
TAGCGTAA	(SEQ ID NO : 15)					2528

FIGURE 18

CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS	QKEGIAEQI	50
VIKITDQGYV	TSHGDHYHYH	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	100
EVKGGYIIKV	DGKYVYVLKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	150
VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	200
ELAAAKAHLA	GKNMQPSQLS	YSSTPSPSLP	INPGTSHEKH	EEDGYGFDAN	250
RIIAEDES GF	VMSHGDHNYH	FFKKDLTEEQ	IKAAQKHLEE	VKTSHNGLDS	300
LSSHEQDYP	NAKEMKDLDK	KIEEKIAGIM	KQYGVKRESI	VVNKEKNAIL	350
YPHGDHHDH	PIDEHKPVGI	GHSNSNYELF	KPEEGVAKKE	GNKVYTGEEL	400
TNVVNLLKNS	TFNNQNFTLA	NGQKRVSFSF	PPELEKKLGI	NMLVKLITPD	450
GKVLEKVS GK	VFGEVGGNIA	NFELDQPYLP	GOTFKYTIAS	KDYPEVS YDG	500
TFTVPTSLAY	KMASQTIFYP	FHAGDTYLRV	NPQFAVPKGT	DALVRVFDEF	550
HGNAYLENNY	KVGEIKLPI	KLNOGTTRTA	GNKIPVTFMA	NAYLDNQSTY	600
IVEVPILEKE	NQTDKPSILP	QFKRNKAQEN	SKLDEKVEEP	KTSEKVEKEK	650
LSETGNSTSN	STLEEVPTVD	PVQEKVAKFA	ESYGMKLENV	LFNMDGTIEL	700
YLPSGEVIKK	NMADFTGEAP	QNGENKPSSE	NGKVSTGTVE	NQPTENKPAD	750
SLPEAPNEKP	VKPNSTDN	MLNPEGNVGS	DPMLDSALEE	APAVDPVQEK	800
LEKFTASYGL	GLDSVIFNMD	GTIELRLPSG	EVIKKNLLIS		840

(SEQ ID NO : 16)

FIGURE 19

CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS	QKEGIAEQI	50
VIKITDQGYV	TSHGDHYHYH	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	100
EVKGGYIIKV	DGKYVYVLKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	150
VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	200
ELAAAKAHLA	GKNMQPSQLS	YSSTASDNMT	QSVAKGSTSK	PANKSENLOS	250
LLKELYDSPS	AQRYSESDGL	VFDPAKIISR	TPNGVAIPHG	DHYHFIPYSK	300
LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	VSSLGSLSSN	PSSLTTSKEL	350
SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	HYIPKSNQIG	QPTLPNNSLA	400
TPSPSLPINP	GTSHEKHEED	GYGFDANRII	AEDESGFVMS	HGDHNYFFK	450
KDLTEEQIKA	AQKHLEEVKT	SHNGLDSLSS	HEQDYPGNAK	EMKDLDKKIE	500
EKIAGIMKQY	GVKRESIVVN	KEKNAIIPYH	GDHHDADPID	EHKPVGIGHS	550
HSNYELFKPE	EGVAKKEGK	VYTGEELTNV	VNLLKNSTFN	NQNFTLANGQ	600
KRVSFSPFPE	LEKKLGINML	VKLITPDGKV	LEKVS GKVFG	EGVGNIANFE	650
LDQPYLPQGT	FKYTIASKDY	PEVSYDGTFT	VPTSLAYKMA	SQTIFYPFHA	700
GDYTLRVNPQ	FAVPKGTDAL	VRVFDEFHGN	AYLENNYKVG	EIKLPIPKLN	750
QGTTRTAGNK	IPVTFMANAY	LDNQSTYIVE	VPILEKENQT	DKPSILPQFK	800
RNKAQENSKL	DEKVEEPKTS	EKVEKEKLSE	TGNSTSNSTL	EEVPTVDPVQ	850
EKVAKFAESY	GMKLENVLFN	MDGTIELYLP	SGEVIKNMA	DFTGEAPQGN	900
GENKPSENGK	VSTGTVENQP	TENKPADSLP	EAPNEKPKVP	ENSTDNMGLN	950
PEGNVGSDPM	LDPAL EEAPA	VDPVQEKLEK	FTASYGLGLD	SVIFNMDGTI	1000
ELRLPSGEVI	KKNLSDFIA				1019

(SEQ ID NO : 55)

FIGURE 20

CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS	QKEGIQAEQI	50
VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	100
EVKGGYIIV	DGKYVYVLKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	150
VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	200
ELAAAKAHLA	GKNMQPSQLS	YSSTASDNNT	QSVAKGSTSK	PANKSENLOS	250
LLKELYDSPS	AQRYSESDGL	VFDPAKIISR	TPNGVAIPHG	DHYHFIPYSK	300
LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	VSSLGSLSSN	PSSLTTSKEL	350
SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	HYIPKSNQIG	QPTLPNNSLA	400
TPSPSLPINP	GTSHEKHEED	GYGFDANRII	AEDESGFVMS	HGDHNHYFFK	450
KDLTEEQIKA	AQKHLEEVKT	SHNGLDSLSS	HEQDYPGNA		489

(SEQ ID NO : 56)

FIGURE 21

MKFSKKYIAA	GSIVIVSLSL	CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS	60
QKEGIQAEQI	VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	120
EVKGGYIIV	DGKYVYVLKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	VAVARSQGRY	180
TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	ELAAAKAHLA	GKNMQPSQLS	240
YSSTASDNNT	QSVAKGSTSK	PANKSENLOS	LLKELYDSPS	AQRYSESDGL	VFDPAKIISR	300
TPNGVAIPHG	DHYHFIPYSK	LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	VSSLGSLSSN	360
PSSLTTSKEL	SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	HYIPKSNQIG	QPTLPNNSLA	420
TPSPSLPINP	GTSHEKHEED	GYGFDANRII	AEDESGFVMS	HGDHNHYFFK	KDLTEEQIKA	480
AQKHLEEVKT	SHNGLDSLSS	HEQDYPGNA				509

(SEQ ID NO : 57)

FIGURE 22

DLTEEQIKAA	QKHLEEVKTS	HNGLDSLSSH	EQDYPGNAKE	MKDLDKKIEE	50
KIAGIMKQYG	VKRESIVVNK	EKNAIYPHG	DHHHADPIDE	HKPVGIGHSH	100
SNYELFKPEE	GVAKKEGNKV	YTGEELTNVV	NLLKNSTFNN	QNFTLANGQK	150
RVSFSFPPEL	EKKLGINMLV	KLITPDGKVL	EKVSGKVFG	GVGNIANFEL	200
DQPYLPQGTF	KYTIASKDYP	EVSYDGTFTV	PTSLAYKMAS	QTIFYPPHAG	250
DTYLRVNPQF	AVPKGTDALV	RVFDEFHGNA	YLENNYKVG	IKLPIPKLNQ	300
GTTRTAGNKI	PVTFMANAYL	DNQSTYIVEV	PILEKENQTD	KPSILPQFKR	350
NKAQENSKLD	EKVEEPTSE	KVEKEKLSET	GNSTSNSTLE	EVPTVDPVQE	400
KVAKFAESYG	MKLENVLFNM	DGTIELYLPS	GEVIKKNMAD	FTGEAPQNG	450
ENKPSSENGKV	STGTVENQPT	ENKPADSLPE	APNEKPVKPE	NSTDNGMLNP	500
EGNVGSDPML	DPALEEAPAV	DPVQEKLEKF	TASYGLGLDS	VIFNMDGTIE	550
LRLPSGEVIK	KNLSDFIAKL	RYRSNHWVPD	SRPEEPSQP	TPEPSPSPQP	600
APNPQPAPSN	PIDEKLVKEA	VRKVGDDYVF	EENGVSRYIP	AKNLSAETAA	650
GIDSKLAKQE	SLSHKLGAKK	TDLPSDDREF	YNKAYDLLAR	IHQDLLDNKG	700
RQVDFEALDN	LLERLKDVS	DKVKLVDDIL	AFLAPIRHPE	RLGKPNQAQIT	750
YTDDEIQVAK	LAGKYTTEDG	YIFDPRDITS	DEGDAYVTPH	MTHSHWIKKD	800
SLSEAERAAA	QAYAKEKGLT	PPSTDHQDSG	NTEAKGAEAI	YNRVKAAKKV	850
PLDRMPYNLQ	YTVEVKNGSL	IIPHYDHYHN	IKFEWFDEGL	YEAPKGYTLE	900
DLATVKYIV	EHPNERPHSD	NGFGNASDHV	QRNKNQADT	QTEKPSEEK	950
PQTEKPEEET	PREEKPQSEK	PESPKPTEEP	EEESPREESE	PQVETEKVEE	1000
KLREAEDLQ	KIQDPIIKSN	AKETLTGLKN	NLLFGTQDNN	TIMAEAEKLL	1050
ALLKESK					1057

(SEQ ID NO : 58)

FIGURE 23

CAYALNQHRS QENKDNRRVS YVDGSQSSQK SENLTPDQVS QKEGIAEQI	50
VIKITDQGYV TSHGDHYHY NGKVPYDALF SEELLMKDPN YQLKDADIVN	100
EVKGGYIKV DGKYYVYLKD AAHADNVRTK DEINRQKQEH VKDNEKVNSN	150
VAVARSQGRY TTNDGYVFNP ADIIEDTGNA YIVPHGGHYH YIPKSDLSAS	200
ELAAA (SEQ ID NO : 59)	205

FIGURE 24

CAYELGLHQA QTVKENNRVS YIDGKQATQK TENLTPDEV S KREGINAEQI	50
VIKITDQGYV TSHGDHYHY NGKVPYDAII SEELLMKDPN YQLKDS DIVN	100
EIKGGYVIKV NGKYYVYLKD AAHADNVRTK EEINRQKQEH SQHREGG TSA	150
NDGAVAFARS QGRYTTDDGY IFNASDIIED TGDAYIVPHG DHYHYIPKNE	200
LSASELAAAE AFLSGRENLS NLR TYRRQNS DNTPR TNWVP SVSNPGTTNT	250
NTSNNSNTNS QASQSN DIDS LLKQLYKLPL SQRHVESDGL IFDPAQITSR	300
TARGVAVPHG NHYHFIPYEQ MSELEKRIAR IIP LRYRSNH WVPDSRPEEP	350
SPQPTPEPSP SPQPAPNPQP APSNPIDEKL VKEAVRKVGD GYVFEENGVS	400
RYIPAKNLSA ETAAGIDSKL AKQESLSHKL GAKKTDLPSS DREFYNKAYD	450
LLARIHQDLL DNKGRQVDFE ALDNLLERLK DVSSDKVKLV DDILAFLAPI	500
RHPERLGKPN AQITYTDD EI QVAKLAGKYT TEDGYIFDPR DITSDEGDAY	550
VTPHMTSHSHW IKKDSLSEAE RAAQA YAKE KGLTPPSTDH QDSGNT EAKG	600
AEAIYNRVKA AKKVPLDRMP YNLQYTV EVK NGSLIIPHYD HYHNIKFEWF	650
DEGLYEAPKG YTLEDLLATV KYYVEHPNER PHSDNGFGNA SDHVQRNKNG	700
QADTNQTEKP SEEKPQTEKP EESTPREEKP QSEKPESPKP TEEPERESPE	750
ESEEPQVETE KVEEKLREAE DLLGKIQDPI IKSNAKETLT GLKNNLLFGT	800
QDNNTIMAEA EKLLALLKES K ((SEQ ID NO : 60)	821

FIGURE 25

CAYELGLHQA QTVKENNRVS YIDGKQATQK TENLTPDEV S KREGINAEQI	50
VIKITDQGYV TSHGDHYHY NGKVPYDAII SEELLMKDPN YQLKDS DIVN	100
EIKGGYVIKV NGKYYVYLKD AAHADNVRTK EEINRQKQEH SQHREGG TSA	150
NDGAVAFARS QGRYTTDDGY IFNASDIIED TGDAYIVPHG DHYHYIPKNE	200
LSASELAAAE AFLSGRENLS NLR TYRRQNS DNTPR TNWVP SVSNPGTTNT	250
NTSNNSNTNS QASQSN DIDS LLKQLYKLPL SQRHVESDGL IFDPAQITSR	300
TARGVAVPHG NHYHFIPYEQ MSELEKRIAR IIP L	334
(SEQ ID NO : 61)	

FIGURE 26

RYRSNHWVPD SRPEEPSQPQ TPEPSPSPQP APNPQPAPSN PIDEKLVKEA	50
VRKVG DGYVF EENGVSRYIP AKNLSAETAA GIDSKLAKQE SLSHKLGAKK	100
TDLPS SDREF YNKAYDLLAR IHQDLLDNKG RQVDFEALDN LLERLKD VSS	150
DKVKLVDDIL AFLAPIRHPE RLGPNAQIT YTDDEIQVAK LAGKYTTEDG	200
YIFDPRDITS DEGDAYVTPH MTHSHWIKKD SLSEABERAAA QAYAKEKGLT	250
PPSTDHQDSG NTEAKGAEAI YNRVKA AKKV PLDRMPYNLQ YTVEVKNGSL	300
IIPHYDHYHN IKFEWFDEGL YEAPKGYTLE DLLATVKYYV EHPNERPHSD	350
NGFGNASDHV QRKNQQA DT NQTEKPSEK POTEKPEEET PREEKPCSEK	400
PESPKPTREP EEESPEESEE PQVETEKVEE KLREAE DLLG KIQDPIIKSN	450
AKETLTGLKN NLLFGTQDNN TIMAEAEKLL ALLKESK	487
(SEQ ID NO : 62)	

FIGURE 27

AEAFLSGREN	LSNLRTYRRQ	NSDNTPRTNW	VPSVSNPGTT	NTNTSNNSNT	50
NSQASQSNDI	DSLLKQLYKL	PLSQRHVESD	GLIFDPAQIT	SRTARGVAVP	100
HGNHYHFIPY	EQMSELEKRI	ARIIPLYRYS	NHWVPDSRPE	EPSPQPTPEP	150
SPSPQPAPNP	QPAPSNPIDE	KLVKEAVRKV	GDGYVFEENG	VSRYIPAKNL	200
SAETAAGIDS	KLAKQESLSH	KLGAKKTDLP	SSDREFYNKA	YDLLARIHQD	250
LLDNKGRQVD	FEALDNLLER	LKDVSSDKVK	LVDDILAFIA	PIRHPERLGK	300
PNAQITYTDD	EIQVAKLAGK	YTTEDGYIFD	PRDITSDEGD	AYVTPHMTSH	350
HWIKKDSLSE	AERAAAQAYA	KEKGLTPPST	DHQDSGNTEA	KGAEAIYNRV	400
KAAKVKPLDR	MPYNLQYTV	VKNGSLIIPH	YDHYHNIKFE	WFDEGLYEAP	450
KGYTLEDLLA	TVKYVVEHPN	ERPHSDNGFG	NASDHVQRNK	NGQADTNQTE	500
KPSEKPKQTE	KPEETPREE	KPQSEKPESP	KPTPEPEEES	PEESEEPQVE	550
TEKVEEKLRE	AEDLLGKIQD	PIIKSNAKET	LTGLKNNLLF	GTQDNNTIMA	600
EAEKLLALLK	ESK	(SEQ ID NO : 63)			613

FIGURE 28

DLTEEQIKAA	QKHLEEVKTS	HNGLDLSLSSH	EQDYPGNAKE	MKDLDKKIEE	50
KIAGIMKQYG	VKRESIVVNK	EKNAIYYPHG	DHHHADPIDE	HKPVGIGHSH	100
SNYELFKPEE	GVAKKEGNKV	YTGEELTNVV	NLLKNSTFNN	QNFTLANGQK	150
RVSFSFPPEL	EKKLGINMLV	KLITPDGKVL	EKVSGKVFGE	GVGNIANFEL	200
DQPYLPGQTF	KYTIASKDYP	EVSYDGTFTV	PTSLAYKMAS	QTIFYPPFHAG	250
DTYLRVNPQF	AVPKGTDALV	RVFDEFHGNA	YLENNYKVGE	IKLPIPKLNQ	300
GTTTRTAGNKI	PVTTFMANAYL	DNQSTYIVEV	PILEKENQTD	KPSILPQFKR	350
NKAQENSKLD	EKVEEPTSE	KVEKEKLSET	GNSTSNSTLE	EVPTVDPVQE	400
KVAKFAESYG	MKLENVLFNM	DGTIELYLP	GEVIKKNMAD	FTGEAPQNG	450
ENKPSSENGKV	STGTVENQPT	ENKPADSLPE	APNEKPVKPE	NSTDNGMLNP	500
EGNVGSDPML	DPALAEAPAV	DPVQEKLEKF	TASYGLGLDS	VIFNMDGTIE	550
LRLPSGEVIK	KNLSDFIA	(SEQ ID NO : 64)			568

FIGURE 29

DLTEEQIKAA	QKHLEEVKTS	HNGLDLSLSSH	EQDYPGNAKE	MKDLDKKIEE	50
KIAGIMKQYG	VKRESIVVNK	EKNAIYYPHG	DHHHADPIDE	HKPVGIGHSH	100
SNYELFKPEE	GVAKKEGNKV	YTGEELTNVV	NLLKNSTFNN	QNFTLANGQK	150
RVSFSFPPEL	EKKLGINMLV	KLITPDGKVL	EKVSGKVFGE	GVGNIANFEL	200
DQPYLPGQTF	KYTIASKDYP	EVSYDGTFTV	PTSLAYKMAS	QTIFYPPFHAG	250
DTYLRVNPQF	AVPKGTDALV	RVFDEFHGNA	YLENNYKVGE	IKLPIPKLNQ	300
GTTTRTAGNKI	PVTTFMANAYL	DNQSTYIVE	(SEQ ID NO : 65)		329

FIGURE 30

EVPILEKENQ TDKPSILPOF KRKAQENSK LDEKVEEPTK SEKVEKEKLS	50
ETGNSTSNST LEEVPTVDPV QEKVAKFAES YGMKLENVLF NMDGTIELYL	100
PSGEVIKKNM ADFTGEAPOG NGENKPSENG KVSTGTVENQ PTENKPADSL	150
PEAPNEKPVK PENSTDNGML NPEGNVGSDP MLDPALEEAP AVDPVQEKLE	200
KFTASYGLGL DSVIFNMDGT IELRLPSGEV IKKNLSDFIA	240
(SEQ ID NO : 66)	

FIGURE 31

DIDSLLKQLY KLPLSQRHVE SDGLIFDPAQ ITSRTARGVA VPHGNHYHFI	50
PYEQMSELEK RIARIIPLY RSNHWVPDSR PEEPSPOPTP EPSPSPQPAP	100
NPQPAPSNPI DEKLVEAVR KVG DGYVFEE NGVSRYIPAK NLSAETAAGI	150
DSKLAKQESL SHKLGAKKTD LPSSDREFYN KAYDLLARIH QDLLDNKGRQ	200
VDFEALDNLL ERLKDVSSDK VKLVDDILAF LAPIRHPERL GKPNAQITYT	250
DDEIQVAKLA GKYTTEDGYI FDPRDITSDE GDAYVTPHMT HSHWIKKDSL	300
SEAERAAAQA YAKEKGLTPP STDHQDSGNT EAKGAEAIYN RVKAAKKVPL	350
DRMPYNLQYT VEVKNGSLII PHYDHYHNIK FEWFDEGLYE APKGYTLEDL	400
LATVKYYVEH PNERPHSDNG FGNASDHVQR NKNGQADTNQ TEKPSEEKPO	450
TEKPEEETPR EEKQSEKPE SPKPTEEPEE ESPEESEEPQ VETEKVEEKL	500
REAEDLLGKI QDPIIKSNAK ETLTGLKNNL LFGTQDNNTI MAEAEKLLAL	550
LKESK (SEQ ID NO : 67)	555

FIGURE 32

DIDSLLKQLY KLPLSQRHVE SDGLIFDPAQ ITSRTARGVA VPHGNHYHFI	50
PYEQMSELEK RIARIIPLY RSNHWVPDSR PEEPSPOPTP EPSPSPQPAP	100
NPQPAPSNPI DEKLVEAVR KVG DGYVFEE NGVSRYIPAK NLSAETAAGI	150
DSKLAKQESL SHKLGAKKTD LPSSDREFYN KAYDLLARIH QDLLDNKGRQ	200
VDFEALDNLL ERLKDVSSDK VKLVDDILAF LAPIRHPERL GKPNAQITYT	250
DDEIQVAKLA GKYTTEDGYI FDPRDITSDE GDAYVTPHMT HSHWIKKDSL	300
SEAERAAAQA YAKEKGLTPP STDHQDSGNT EAKGAEAIYN RVKAAKKVPL	350
DRMPYNLQYT VEVKNGSLII PHYDHYHNIK FEWFDEGLYE APKGYTLEDL	400
LATVKYYVEH PNERPHSDNG FGNASDHV (SEQ ID NO : 68)	428

FIGURE 33

GLYEAPKGYT LEDLLATVKY YVEHPNERPH SDNGFGNASD HVQRNKGQA	50
DTNQTEKPSE EKPQTEKPER ETPREEKPOS EKPESPKPTE EPSEESPEES	100
EEPQVETEKV EEKLEAEDL L (SEQ ID NO : 69)	121

FIGURE 34

ASDHVQRNKN GQADTNQTEK PSEEKQTEK PEEETPREEK PQSEKPEPK	50
PTEEPPEESP EESEEPQVET EKVEEKLREA EDLLGKIQDP IIKSNAKETL	100
TOLKNNLLFG TQDNNTIMAE AEKLLALLKE SK	132
(SEQ ID NO : 70)	

FIGURE 35

DIDSLKQLY KLPLSORHVE SDGLIFDPAQ ITSRTARGVA VPHGNHYHFI 50
 PYEQMSELEK RIARIIPLY RSNHWVPDSR PEEPSQPTP EPSPSQPAP 100
 NPQPAPSNPI DEKLVKEAVR KVG DGYVFE NGVSRYIPAK NLSAETAAGI 150
 DSKLAKQESL SHKLGA KTD LPSSDREFYN KAYDLLARIH QDLLDNKGRQ 200
 VDFAELDNLL ERLKDVSSDK VKLVDD (SEQ ID NO : 71) 226
 FIGURE 36

DILAF LAPIR HPERLGK PNA QITYTDDEIQ VAKLAGKYTT EDGYIFDPRD 50
 ITSDEGDAYV TPHMTHSHWI KKDSLSEAER AAAQAYAKEK GLTPPSTDHQ 100
 DSGNTEAKGA EAIYNRVKAA KKVPLDRMPY NLQYTEVKV GSLIIPHYDH 150
 YHNIKFEWFD EGLYEAPKGY TLEDLLATVK YYVEHPNERP HSDNGFGNAS 200
 DHV (SEQ ID NO : 72) 203
 FIGURE 37

CSYELGRHQA GOVKKESNRV SYIDGDQAGQ KAENLTPDEV SKREGINAEO 50
 IVIKITDQGY VTSHGDHYHY YNGKVPYDAI ISEELLMKDP NYQLKDS DIV 100
 NEIKGGYVIK VDGKYYVYLK DAAHADNIRT KEEIKRQKQE HSHNHNSRAD 150
 NAAAAARAQ RYTTDDGYIF NASDI EDTG DAYIVPHGDH YHYIPKNELS 200
 ASELA AEAY WNGKQSRPS SSSSYNANPV QPRLSENHNL TVTPTYHQNQ 250
 GENISSLLRE LYAKPLSERH VESDGLIFDP AQITSRTARG VAVPHGNHYH 300
 FIPYEQMSEL EKRIARIIP RYRSNHWVPD SRPEQSPQS TPEPSPSLQP 350
 APNPQPAPSN PIDEKLVKEA VRKVG DGYVFE EENGVSRYIP AKDLSAETAA 400
 GIDSKLAKQE SLSHKLGA KK TDLPSSDREF YNKAYDLLAR IHQDLLDNKG 450
 RQVDFEVL DN LLERLKDVSS DKVKLVDDIL AFLAPIRHPE RLKGPNAQIT 500
 YTDDEIQVAK LAGKYTTEDG YIFDPRDITS DEGDAYVTPH MTHSHWIKKD 550
 SLSEAERAAA QAYAKEKGLT PPSTDHQDSG NTEAKGAEAI YNRVKA AKKV 600
 PLDRMPYNLQ YTVEVKNGSL IIPHYDHYHN IKFEWFDEGL YEAPKGYSLE 650
 DLLATVKYVV EHPNERPHSD NGFGNASDHV RKNKADQDSK PDEDKEHDEV 700
 SEPTHPESDE KENHAGLNPS ADNLYKPSTD TEETEEEAED TDEAEIPQV 750
 ENSVINAKIA DAEALLEKVT DPSIRQNAME TLTKLKSSLL LGTKDNNTIS 800
 AEVDSLLALL KESQPAPIQ (SEQ ID NO : 73) 819
 FIGURE 38

ENISSLLREL YAKPLSERHV ESDGLIFDPA QITSRTARGV AVPHGNHYHF 50
 IPYEQMSELE KRIARIIPLR YRSNHWVPDS RPEQSPQST PEPSPSLQPA 100
 PNPQPAPSNP IDEKLVKEAV RKVG DGYVFE EENGVSRYIPA KDLAETAAG 150
 IDSKLAKQES LSHKLGA KKT DLPSSDREFY NKAYDLLARI HQDLLDNKGR 200
 QVDFEVL DN LERLKDVSSD KVKLVDDILA FLAPIRHPE LGKPNAQITY 250
 TDDEIQVAKL AGKYTTEDGY IFDPRDITS EGDAYVTPHM THSHWIKKDS 300
 LSEAERAAAQ AYAKEKGLTP PSTDHQDSGN TEAKGAEAIY NRVKA AKKV 350
 LDRMPYNLQY TVEVKNGSLI IIPHYDHYHNI KFEWFDEGLY EAPKGYSLED 400
 LLATVKYVVE HPNERPHSDN GFGNASDHVR KKNKADQDSK DEDKEHDEVS 450
 EPTHPESDEK ENHAGLNPSA DNLYKPSTD EETEEEAEDT TDEAEIPQVE 500
 NSVINAKIAD AEALLEKVTD PSIRQNAME LTGLKSSLL GTKDNNTISA 550
 EVDSLLALLK ESQPAPIQ (SEQ ID NO : 74) 568
 FIGURE 39

VRKNKADQDS KPDEDKEHDE VSEPTHPESD EKENHAGLNP SADNLYKPST 50
 DTEETEEAE DTTDEAEIPQ VENSVINAKI ADAEALLEKV TDPSIRQNAM 100
 ETLTGLKSSL LLGTDKNNTI SAEVDSLLAL LKESQPAPIQ 140
 (SEQ ID NO : 75)

FIGURE 40

GACTTGACAG AAGAGCAAAT TAAGGCTGCG CAAAAACATT TAGAGGAAGT 50
 TAAACTAGT CATAATGGAT TAGATTCTTT GTCATCTCAT GAACAGGATT 100
 ATCCAGGTAA TGCCAAAGAA ATGAAAGATT TAGATAAAAA AATCGAAGAA 150
 AAAATTGCTG GCATTATGAA ACAATATGGT GTCAAACGTG AAAGTATTGT 200
 CGTGAAATAAA GAAAAAAATG CGATTATTTA TCCGCATGGA GATCACCATC 250
 ATGCAGATCC GATTGATGAA CATAAACCGG TTGGAATTGG TCATTCTCAC 300
 AGTAACTATG AACTGTTTAA ACCCGAAGAA GGAGTTGCTA AAAAGAAGG 350
 GAATAAAGTT TATACTGGAG AAGAATTAAC GAATGTTGTT AATTTGTTAA 400
 AAAATAGTAC GTTTAATAAT CAAAACCTTA CTCTAGCCAA TGGTCAAAAA 450
 CGCGTTTCTT TTAGTTTTCC GCCTGAATTG GAGAAAAAAT TAGGTATCAA 500
 TATGCTAGTA AAATTAATAA CACCAGATGG AAAAGTATTG GAGAAAGTAT 550
 CTGGTAAAGT ATTTGGAGAA GGAGTAGGGA ATATTGCAAA CTTTGAAATTA 600
 GATCAACCTT ATTTACCAGG ACAAACATTT AAGTATACTA TCGCTTCAAA 650
 AGATTATCCA GAAGTAAGTT ATGATGGTAC ATTTACAGTT CCAACCTCTT 700
 TAGCTTACAA AATGGCCAGT CAAACGATTT TCTATCCTTT CCATGCAGGG 750
 GATACTTATT TAAGAGTGAA CCCTCAATTT GCAGTGCCTA AAGGAACTGA 800
 TGCTTTAGTC AGAGTGTTTG ATGAATTTCA TGGAAATGCT TATTTAGAAA 850
 ATAACATAAA AGTTGGTGAA ATCAAATTAC CGATTCCGAA ATTAAACCAA 900
 GGAACAACCA GAACGGCCGG AAATAAAATT CCTGTAACCT TCATGGCAAA 950
 TGCTTATTTG GACAATCAAT CGACTTATAT TGTGGAAGTA CCTATCTTGG 1000
 AAAAAAGAAA TCAAACTGAT AAACCAAGTA TTCTACCACA ATTTAAAGG 1050
 AATAAAGCAC AAGAACTC AAAACTTGAT GAAAAGGTAG AAGAACCAAA 1100
 GACTAGTGAG AAGGTAGAAA AAGAAAAACT TTCTGAACT GGAATAGTA 1150
 CTAGTAATTC AACGTTAGAA GAAGTTCCTA CAGTGGATCC TGTACAAGAA 1200
 AAGTAGCAA AATTTGCTGA AAGTTATGGG ATGAAGCTAG AAAATGTCTT 1250
 GTTTAATATG GACGGAACAA TTGAATTATA TTTACCATCA GGAGAAGTCA 1300
 TTAAGAGAA TATGGCAGAT TTACAGGAG AAGCACCTCA AGGAAATGGT 1350
 GAAAATAAAC CATCTGAAAA TGGAAAAGTA TCTACTGGAA CAGTTGAGAA 1400
 CCAACCAACA GAAAATAAAC CAGCAGATTC TTTACCAGAG GCACCAACG 1450
 AAAACCTGT AAAACCAGAA AACTCAACGG ATAATGGAAT GTTGAATCCA 1500
 GAAGGGAATG TGGGGAGTGA CCCTATGTTA GATCCAGCAT TAGAGGAAGC 1550
 TCCAGCAGTA GATCCTGTAC AAGAAAAATT AGAAAAATTT ACAGCTAGTT 1600
 ACGGATTAGG CTTAGATAGT GTTATATTCA ATATGGATGG AACGATTGAA 1650
 TTAAGATTGC CAAGTGAGAA AGTGATAAAA AAGAATTTAT CTGATTTCAT 1700
 AGCGAAGCTT CGTTATCGTT CAAACCATTG GGTACCAGAT TCAAGACCAG 1750
 AAGAACCAAG TCCACAACCG ACTCCAGAAC CTAGTCCAAG TCCGCAACCT 1800
 GCACCAATC CTCAACCAGC TCCAAGCAAT CCAATTGATG AGAAATTGGT 1850
 CAAAGAAGCT GTTCGAAAAG TAGGCGATGG TTATGTCTTT GAGGAGAATG 1900
 GAGTTTCTCG TTATATCCCA GCCAAGAATC TTTCAGCAGA AACAGCAGCA 1950
 GGCATTGATA GCAAACTGGC CAAGCAGGAA AGTTTATCTC ATAAGCTAGG 2000
 AGCTAAGAAA ACTGACCTCC CATCTAGTGA TCGAGAATTT TACAATAAGG 2050
 CTTATGACTT ACTAGCAAGA ATTCACCAAG ATTTACTTGA TAATAAAGGT 2100
 CGACAAGTTG ATTTTGAGGC TTTGGATAAC CTGTTGGAAC GACTCAAGGA 2150
 TGTCTCAAGT GATAAAGTCA AGTTAGTGGA TGATATTCTT GCCTTCTTAG 2200
 CTCCGATTCTG TCATCCAGAA CGTTTAGGAA AACCAAATGC GCAAATTACC 2250
 TACACTGATG ATGAGATTCA AGTAGCCAAG TTGGCAGGCA AGTACACAAC 2300
 AGAAGACGGT TATATCTTTG ATCCTCGTGA TATAACCAAG GATGAGGGGG 2350
 ATGCCATGT AACTCCACAT ATGACCCATA GCCACTGGAT TAAAAAGAT 2400

AGTTTGTCTG	AAGCTGAGAG	AGCGGCAGCC	CAGGCTTATG	CTAAAGAGAA	2450
AGGTTTGACC	CCTCCTTCGA	CAGACCATCA	GGATTTCAGGA	AATACTGAGG	2500
CAAAAGGAGC	AGAAGCTATC	TACAACCGCG	TGAAAGCAGC	TAAGAAGGTG	2550
CCACTTGATC	GTATGCCTTA	CAATCTTCAA	TATACTGTAG	AAGTCAAAAA	2600
CGGTAGTTTA	ATCATACCTC	ATTATGACCA	TTACCATAAC	ATCAAATTTG	2650
AGTGGTTTGA	CGAAGGCCTT	TATGAGGCAC	CTAAGGGGTA	TACTCTTGAG	2700
GATCTTTTGG	CGACTGTCAA	GTACTATGTC	GAACATCCAA	ACGAACGTCC	2750
GCATTGAGAT	AATGGTTTTG	GTAACGCTAG	CGACCATGTT	CAAAGAAACA	2800
AAAATGGTCA	AGCTGATACC	AATCAAACGG	AAAAACCAAG	CGAGGAGAAA	2850
CCTCAGACAG	AAAAACCTGA	GGAAGAAACC	CCTCGAGAAG	AGAAACCACA	2900
AAGCGAGAAA	CCAGAGTCTC	CAAAACCAAC	AGAGGAACCA	GAAGAAGAAT	2950
CACCAGAGGA	ATCAGAAGAA	CCTCAGGTCG	AGACTGAAAA	GGTTGAAGAA	3000
AAACTGAGAG	AGGCTGAAGA	TTTACTTGGA	AAAATCCAGG	ATCCAATTAT	3050
CAAGTCCAAT	GCCAAAGAGA	CTCTCACAGG	ATTAATAAAT	AATTTACTAT	3100
TTGGCACCCA	GGACAACAAT	ACTATTATGG	CAGAAGCTGA	AAAACATTG	3150
GCTTTATTAA	AGGAGAGTAA	G	(SEQ ID NO : 76)		3171

FIGURE 41

EAYWNGKQGS	RPSSSSSYNA	NPVQPRLSN	HNLTVTPTYH	ONQGENISSL	50
LRELYAKPLS	ERHVESDGLI	FDPAQITSRT	ARGVAVPHGN	HYHFIPYEQM	100
SELEKRIARI	IPLRYRSNHW	VPDSRPEQPS	POSTPEPSPS	LQPAPNPQPA	150
PSNPIDEKLV	KEAVRKVDG	YVFEENGVS	YIPAKDLSAE	TAAGIDSKLA	200
KQESLSHKL	AKKTDLPSSD	REFYNKAYDL	LARIHQDLLD	NKGRQVDFEV	250
LDNLLERLKD	VSSDKVKLVD	DILAFLAPIR	HPERLGKPNA	QITYTDDEIQ	300
VAKLAGKYTT	EDGYIFDPRD	ITSDEGDAYV	TPHMTSHWI	KKDSLSEAR	350
AAAQAYAKEK	GLTPPSTDHQ	DSGNTAKGA	EAIYNRVKAA	KKVPLDRMPY	400
NLQYTVKVN	GSLIIPHYDH	YHNIKFEWFD	EGLYEAPKGY	SLEDLLATVK	450
YYVEHPNERP	HSDNGFGNAS	DHV	(SEQ ID NO : 77)		473

FIGURE 42

CAYALNQHRS	QENKDNRRVS	YVDGSQSSQK	SENLTDPQVS	QKEGIAEQI	50
VIKITDQGYV	TSHGDHYHY	NGKVPYDALF	SEELLMKDPN	YQLKDADIVN	100
EVKGGYIIKV	DGKYVYVLKD	AAHADNVRTK	DEINRQKQEH	VKDNEKVNSN	150
VAVARSQGRY	TTNDGYVFNP	ADIIEDTGNA	YIVPHGGHYH	YIPKSDLSAS	200
ELAAAKAHLA	GKNMQPSQLS	YSSTASDNNT	QSVAKGSTSK	PANKSENLOS	250
LLKELYDSPS	AQRYSEDGL	VFDPAKIISR	TPNGVAIPHG	DHYHFIPYSK	300
LSALEEKIAR	MVPISGTGST	VSTNAKPNEV	VSSLGSLSSN	PSSLTTSKEL	350
SSASDGYIFN	PKDIVEETAT	AYIVRHGDHF	HYIPKSNQIG	QPTLPNNSLA	400
TPSPSLPINP	GTSHEKHEED	GYGFDANRII	AEDESGFVMS	HGDHNNHYFFK	450
KDLTEEQIKA	AQKHLEEVKT	SHNGLDSLSS	HEQDYPGNAK	EMKDLDKKIE	500
EKIAGIMKQY	GVKRESIVVN	KEKNAIYPH	GDHHHADPID	EHKPVGIGHS	550
HSNYELFKPE	EGVAKKEGK	VYTGEELTNV	VNLLKNSTFN	NQNFTLANGQ	600
KRVSFSPFPE	LEKKLGINML	VKLITPDGKV	LEKVSQKVFG	EGVGNIANFE	650
LDQPYLPGQT	FKYTIASKDY	PEVSYDGTFT	VPTSLAYKMA	SQTIFYPFHA	700
GDTYLRVNPQ	FAVPKGTDAL	VRVFDEFHGN	AYLENNYKVG	EIKLPIPKLN	750
QGTTRTAGNK	IPVTFMANAY	LDNQSTYIVE	(SEQ ID NO : 78)		780

FIGURE 43

CAYELGLHQA	QTVKENNRVS	YIDGQATQK	TENLTPDEVS	KREGINAEQI	50
VIKITDQGYV	TSHGDHYHY	NGKVPYDAII	SEELLMKDPN	YQLKDSDIVN	100
EIKGGYVIKV	NGKYVYVLKD	AAHADNVRTK	EEINRQKQEH	SOHREGGTS	150
NDGAVAFARS	QGRYTTDDGY	IFNASDIED	TGDAYIVPHG	DHYHYIPKNE	200
LSASELAAAE	AFLSGRENLS	NLRTYRRQNS	DNTPRTNWVP	SVSNPGTTNT	250
NTSNNSTNS	QASQSNIDS	LLKQLYKLPL	SQRHVESDGL	IFDPAQITSR	300
TARGVAVPHG	NHYHFIPYEQ	MSELEKRIAR	IIPLYRSNH	WVPDSRPEEP	350
SPQPTPEPSP	SPQPAPNPQP	APSNPIDKEL	VKEAVRKVGD	GYVFEENGVS	400
RYIPAKNLSA	ETAAGIDSKL	AKQESLSHKL	GAKKTDLPSS	DREFYNKAYD	450
LLARIHQDLL	DNKGRQVDFE	ALDNLLERLK	DVSSDKVKLV	DDILAFLAPI	500
RHPERLGKPN	AQITYTDDDEI	QVAKLAGKYT	TEDGYIFDPR	DITSDEGDAY	550
VTPHMTSHSW	IKKDSLSEAE	RAAAQAYAKE	KGLTPPSTDH	QDSGNTAEAG	600
AEAIYNRVKA	AKKVPLDRMP	YNLQYTVEVK	NGSLIIPHYD	HYHNIKFEWF	650
DEGLYEAPKG	YTLEDLLATV	KYYVEHPNER	PHSDNGFGNA		690

(SEQ ID NO : 79.)

FIGURE 44

GTGAAGAAAA	CATATGGTTA	TATCGGCTCA	GTTGCTGCCA	TTTTACTAGC	TACTCATATT	60
GGAAGTTACC	AACTTGGTAA	GCATCATATG	GGTCTAGCAA	CAAAGGACAA	TCAGATTGCC	120
TATATTGATG	ACAGCAAAGG	TAAGGCAAAA	GCCCCTAAAA	CAAAACAAAAC	GATGGATCAA	180
ATCAGTGCTG	AAGAAGGCAT	CTCTGCTGAA	CAGATCGTAG	TCAAAATTAC	TGACCAAGGC	240
TATGTGACCT	CACACGGTGA	CCATTATCAT	TTTTACAATG	GGAAAGTTCC	TTATGATGCG	300
ATTATTAGTG	AAGAGTTGTT	GATGACGGAT	CCTAATTACC	GTTTTAAACA	ATCAGACGTT	360
ATCAATGAAA	TCTTAGACGG	TTACGTTATT	AAAGTCAATG	GCAACTATTA	TGTTTACCTC	420
AAGCCAGGTA	GTAAGCGCAA	AAACATTCTA	ACCAAACAAC	AAATTGCTGA	GCAAGTAGCC	480
AAAGGAACCT	AAGAAGCTAA	AGAAAAAGGT	TTAGTCAAG	TGGCCCATCT	CAGTAAAGAA	540
GAAGTTGCGG	CAGTCAATGA	AGCAAAAAGA	CAAGGACGCT	ATACTACAGA	CGATGGCTAT	600
ATTTTTAGTC	CGACAGATAT	CATTGATGAT	TTAGGAGATG	CTTATTTAGT	ACCTCATGGT	660
AATCACTATC	ATTATATTCC	TAAAAAGGAT	TTGTCTCCAA	GTGAGCTAGC	TGCTGCACAA	720
GCCTACTGGA	GTCAAAAACA	AGGTCGAGGT	GCTAGACCGT	CTGATTACCG	CCCGACACCA	780
GCCCCAGGTC	GTAGGAAAGC	CCCAATTCCCT	GATGTGACGC	CTAACCTTGG	ACAAGGTCAT	840
CAGCCAGATA	ACGGTGGCTA	TCATCCAGCG	CCTCCTAGGC	CAAATGATGC	GTCAACAAAAC	900
AAACACCAAA	GAGATGAGTT	TAAAGGAAAA	ACCTTTAAGG	AACTTTTAGA	TCAACTACAC	960
CGTCTTGATT	TGAAATACCG	TCATGTGGAA	GAAGATGGGT	TGATTTTTGA	ACCGACTCAA	1020
GTGATCAAAT	CAAACGCTTT	TGGGTATGTG	GTGCCTCATG	GAGATCATT	TCATATTATC	1080
CCAAGAAGTC	AGTTATCACC	TCTTGAAATG	GAATTAGCAG	ATCGATACTT	AGCTGGCCAA	1140
ACTGAGGACA	ATGACTCAGG	TTCAGAGCAC	TCAAAACCAT	CAGATAAAGA	AGTGACACAT	1200
ACCTTTCTTG	GTCATCGCAT	CAAAGCTTAC	GGAAAAGGCT	TAGATGGTAA	ACCATATGAT	1260
ACGAGTGATG	CTTATGTTTT	TAGTAAAGAA	TCCATTCAAT	CAGTGGATAA	ATCAGGAGTT	1320
ACAGCTAAAC	ACGGAGATCA	TTTCCACTAT	ATAGGATTTG	GAGAACTTGA	ACAATATGAG	1380
TTGGATGAGG	TCGCTAACTG	GGTGAAAGCA	AAAGGTCAAG	CTGATGAGCT	TGCTGCTGCT	1440
TTGGATCAGG	AACAAGGCAA	AGAAAAACCA	CTCTTTGACA	CTAAAAAAGT	GAGTCGCAAA	1500
GTAACAAAAG	ATGGTAAAGT	GGGCTATATG	ATGCCAAAAG	ATGGTAAGGA	CTATTTCTAT	1560
GCTCGTGATC	AACTTGATTT	GACTCAGATT	GCCTTTGCCG	AACAAGAACT	AATGCTTAA	1620
GATAAGAAGC	ATTACCGTTA	TGACATTGTT	GACACAGGTA	TTGAGCCACG	ACTTGCTGTA	1680
GATGTGTCAA	GTCTGCCGAT	GCATGCTGGT	AATGCTACTT	ACGATACTGG	AAGTTCGTTT	1740
GTTATCCAC	ATATTGATCA	TATCCATGTC	GTTCCGTATT	CATGGTTGAC	GCGCGATCAG	1800
ATTGCAACAG	TCAAGTATGT	GATGCAACAC	CCCGAAGTTC	GTCCGGATGT	ATGGTCTAAG	1860
CCAGGGCATG	AAGAGTCAGG	TTCCGGTCATT	CCAAATGTTA	CGCCTCTTGA	TAAACGTGCT	1920
GGTATGCCAA	ACTGGCAAAT	TATCCATTCT	CGGCTATATT	TTCGATCCAC	TTCAAAAAGC	1980
GGTCGTTTTG	CAACACCAGA	CGGCTATATT	TTCCGTTAGC	ATCCCAAGAG	CAGATGGCAG	2040
ACTTTTGTAT	GGAAAGATGG	CTCCTTTAGC	ATCCCAAGCT	GAGTGGCAAC	AAGCTCAAGA	2100
ACCATTAAATA	AATCTGATCT	ATCCCAAGCT	GAGTGGCAAC	AAGCTCAAGA	GTTATTGGCA	2160
AAGAAAAATA	CTGGTGATGC	TACTGATACG	GATAAACCCA	AAGAAAAAGCA	ACAGGCAGAT	2220
AAGAGCAATG	AAAACCAACA	GCCAAGTGAA	GCCAGTAAAG	AAGAAAAAGA	ATCAGATGAC	2280
TTTATAGACA	GTTTACCAGA	CTATGGTCTA	GATAGAGCAA	CCCTAGAAGA	TCATATCAAT	2340
CAATTAGCAC	AAAAAGCTAA	TATCGATCCT	AAGTATCTCA	TTTTCCAACC	AGAAGGTGTC	2400
CAATTTTATA	ATAAAAATGG	TGAATTGGTA	ACTTATGATA	TCAAGACACT	TCAACAAATA	2460
AACCCTTAA	(SEQ ID NO : 80)					2469

FIGURE 45

VKKTYGYIGS	VAAILLATHI	GSYQLGKHHM	GLATKDNQIA	YIDDSKGKAK	50
APKTNKTMDO	ISAEEGISAE	QIVVKITDQG	YVTSBGDHYH	FYNGKVPYDA	100
IISEELLMTD	PNYRFKQSDV	INEILDGYVI	KVNGNYVYVL	KPGSKRKNIR	150
TKQQIAEQVA	KGTKEAKEKG	LAQVAHLSKE	EVAAVNEAKR	QGRYTTDDGY	200
IFSPTDIIDD	LGDAYLVPHG	NHYHYIPKKD	LSPSELAAQA	AYWSQKQGRG	250
ARPSDYRPTP	APGRRKAPIP	DVTPNPGQGH	QPDNGGYHPA	PPRPNDASQN	300
KHQRDEFKGG	TFKELLDQLH	RDLKRYHVE	EDGLIFEPTQ	VIKSNAFGYV	350
VPHGDHYHII	PRSQLSPLEM	ELADRYLAGQ	TEDNDGSEH	SKPSDKEVTH	400
TFLGHRIKAY	GKGLDGKPYD	TSDAYVFSKE	SIHSVDKSGV	TAKHGDHFHY	450
IGFGELEQYE	LDEVANWVKA	KGQADELAAA	LDQEQGKEKP	LFDTKKVSRL	500
VTKDGGKGYM	MPKDGKDYFY	ARDQLDLTQI	AFAEQELMLK	DKKHYRYDIV	550
DTGIEPRLAV	DVSSLPMHAG	NATYDTGSSF	VIPHIDHIHV	VPYSWLTRDQ	600
IATVKYVMQH	PEVRPDVWSK	PGHEESGSKI	PNVTPLDKRA	GMPNWQIHS	650
AEEVQKALAE	GRFATPDGYI	FDPRDVLAK	TFVWKDGSFS	IPRADGSSLR	700
TINKSDLSQA	EWQQAQELLA	KKNTGDATDT	DKPKEKQAD	KSNNQPPSE	750
ASKEEKESDD	FIDSLPDYGL	DRATLEDHIN	QLAQKANIDP	KYLIFQPEGV	800
QFYNKNGELV	TYDIKTLQOI	NPP	(SEQ ID NO : 81)		823

FIGURE 46

GTGAAGAAAA	CATATGGTTA	TATCGGCTCA	GTTGCTGCCA	TTTTACTAGC	TACTCATATT	60
GGAAGTTACC	AACTTGGTAA	GCATCATATG	GGTCTAGCAA	CAAAGGACAA	TCAGATTGCC	120
TATATTGATG	ATAGCAAAGG	TAAGGCAAAA	GCCCCTAAAA	CAAACAAAAC	GATGGATCAA	180
ATCAGTGTCTG	AAGAAGGCAT	CTCTGCTGAA	CAGATCGTAG	TCAAAATTAC	TGACCAAGGT	240
TATGTGACCT	CACACGGTGA	CCATTATCAT	TTTTACAATG	GGAAAGTTCC	TTATGATGCG	300
ATTATTAGTG	AAGAGTTGTT	GATGACGGAT	CCTAATTACC	ATTTTAAACA	ATCAGACGTT	360
ATCAATGAAA	TCTTAGACGG	TTACGTTATT	AAAGTCAATG	GCAACTATTA	TGTTTACCTC	420
AAGCCAGGTA	GTAAGCGCAA	AAACATTCTGA	ACCAAACAAC	AAATTGCTGA	GCAAGTAGCC	480
AAAGGAACTA	AAGAAGCTAA	AGAAAAAGGT	TTAGTCAAG	TGGCCCATCT	CAGTAAAGAA	540
GAAAGTTGCGG	CAGTCAATGA	AGCAAAAAGA	CAAGGACGCT	ATACTACAGA	CGATGGCTAT	600
ATTTTGTATC	CGACAGATAT	CATTGATGAT	TTAGGAGACG	CTTATTTAGT	ACCTCATGGT	660
AATCACTATC	ATTATATTCC	TAAAAAAGAT	TTGTCTCCAA	GTGAGCTAGC	TGCTGCACAA	720
GCTTACTGGA	GTCAAAAACA	AGGTGAGGT	GCTAGACCGT	CTGATTACCG	CCCGACACCA	780
GCCCCAGGTC	GTAGGAAAGC	TCCAATTCCCT	GATGTGACGC	CTAACCTGG	ACAAGGTCAT	840
CAGCCAGATA	ACGGTGGCTA	TCATCCAGCG	CCTCTAGGC	CAAATGATGC	GTCAAAAAC	900
AAACACCAAA	GAGATGAGTT	TAAAGGAAAA	ACCTTTAAGG	AACTTTTAGA	TCAACTACAC	960
CGTCTTGATT	TGAAATACCG	TCATGTGGAA	GAAGATGGGT	TGATTTTGA	ACCGACTCAA	1020
GTGATCAAAT	CAACGCTTT	TGGGTATGTG	GTGCCTCATG	GAGATCATT	TCATATTATC	1080
CCAAGAAGTC	AGTTATCACC	TCTTGAAATG	GAATTAGCAG	ATCGATACTT	AGCCGGTCAA	1140
ACTGAGGACA	ATGATTCAGG	TTCAGATCAC	TCAAAACCAT	CAGATAAAGA	AGTGACACAT	1200
ACCTTTCTTG	GTCTATCGCAT	CAAAGCTTAC	GGAAAAGGCT	TAGATGGTAA	ACCATATGAT	1260
ACGAGTGTATG	CTTATGTTTT	TAGTAAAGAA	TCCATTTCATT	CAGTGGATAA	ATCAGGAGTT	1320
ACAGCTAAAC	ACGGAGATCA	TTTCCACTAT	ATAGGATTTG	GAGAACTTGA	ACAATATGAG	1380
TTGGATGAGG	TCGCTAACTG	GGTGAAAGCA	AAAGGTCAAG	CTGATGAGCT	TGCTGCTGCT	1440
TTGGATCAGG	AACAAGGCAA	AGAAAAACCA	CTCTTTGACA	CTAAAAAAGT	GAGTCGCAAA	1500
GTAACAAAAG	ATGGTAAAGT	GGGCTATATT	ATGCCAAAAG	ATGGCAAGGA	CTATTTCAT	1560
GCTCGTGATC	AACTTGATTT	GACTCAGATT	GCCTTTGCCG	AACAAGAAGT	AATGCTTAAA	1620
GATAAGAACC	ATTACCGTTA	TGACATTGTT	GACACAGGTA	TTGAGCCACG	ACTTGCTGTA	1680
GATGTGTCAA	GTCTGCCGAT	GCATGCTGGT	AATGCTACTT	ACGATACTGG	AAGTTCGTTT	1740
GTTATCCCTC	ATATTGATCA	TATCCATGTC	GTTCCGTATT	CATGGTTGAC	GCGCGATCAG	1800
ATTGCAACAA	TCAAGTATGT	GATGCAACAC	CCCGAAGTTC	GTCCAGATGT	ATGGTCTAAG	1860
CCAGGGCATG	AAGAGTCAGG	TTCGGTCATT	CCAAATGTTA	CGCCTCTTGA	TAAACGTGCT	1920
GGTATGCCAA	ATTGGCAAAT	CATCCATTCT	GCTGAAGAAG	TTCAAAAAGC	CCTAGCAGAA	1980
GGTCGTTTTG	CAACACCAGA	CGGCTATATT	TTCGATCCAC	GAGATGTTTT	GGCCAAAGAA	2040
ACTTTTGTAT	GGAAAGATGG	CTCCTTTAGC	ATCCCAAGAG	CAGATGGCAG	TTCATTGAGA	2100
ACCATTAATA	AATCTGATCT	ATCCCAAGCT	GAGTGGCAAC	AAGCTCAAGA	GTTATTGGCA	2160
AAGAAAAACG	CTGGTGATGC	TACTGATACG	GATAAACCCA	AAGAAAAGCA	ACAGGCAGAT	2220
AAGAGCAATG	AAAACCAACA	GCCAAGTGAA	GCCAGTAAAG	AAGAAGAAAA	AGAATCAGAT	2280
GACTTTATAG	ACAGTTTACC	AGACTATGGT	CTAGATAGAG	CAACCCTAGA	AGATCATATC	2340
AATCAATTAG	CACAAAAAGC	TAATATCGAT	CCTAAGTATC	TCATTTTCCA	ACCAGAAGGT	2400
GTCCAATTTT	ATAATAAAAA	TGGTGAATTA	GTAACCTTATG	ATATCAAGAC	GCTTCAACAA	2460
ATAAACCCCT	AA	(SEQ ID NO : 82)				2472

FIGURE 47

VKKTYGYIGS	VAAILLATHI	GSYQLGKHHM	GLATKDNQIA	YIDDSKGKAK	50
APKTNKTMDO	ISAEEGISAE	QIVVKITDOQ	YVTSHGDHYH	FYNGKVPYDA	100
IISEELLMTD	PNYHFKQSDV	INEILDGYVI	KVNGNYVYVL	KPGSKRKNIR	150
TKQQIAEQVA	KGTKEAKEKG	LAQVAHLSKE	EVAAVNEAKR	QGRYTTDDGY	200
IFSPTDIIDD	LGDAYLVPHG	NHYHYIPKOD	LSPSELAAAQ	AYWSQKQGRG	250
ARPSDYRPTP	APGRRKAPIP	DVTPNPGQGH	QPDNGGYHPA	PPRPNDASQN	300
KHORDEFKGG	TFKELLDQLH	RLDLKYRHVE	EDGLIFEPTQ	VIKSNAFGYV	350
VPHGDHYHII	PRSQLSPLEM	ELADRYLAGQ	TEDNDSGSDH	SKPSDKEVTH	400
TFLGHRIKAY	GKGLDGKPYD	TSDAYVFSKE	SIHSVDKSGV	TAKHGDHFHY	450
IGFGELEQYE	LDEVANWVKA	KGQADELAAA	LDQEQGKEKP	LFDTKKVSrk	500
VTKDGVGYI	MPKDGKDYFY	ARDQLDLTQI	AFAEQELMLK	DKNHYRYDIV	550
DTGIEPRLAV	DVSSLPMHAG	NATYDTGSSF	VIPHIDHIHV	VPYSWLTRDQ	600
IATIKYVMQH	PEVRPDVWSK	PGHEESGSKI	PNVTPLDKRA	GMPNWQIIHS	650
ABEVQKALAE	GRFATPDGYI	FDPRDVLAKE	TFVWKDGSFS	IPRADGSSLR	700
TINKSDLSQA	EWQQAQELLA	KKNAGDATDT	DKPKEKQQAD	KSNENQQPSE	750
ASKEEEKESD	DFIDSLPDYG	LDRATLEDHI	NQLAQKANID	PKYLIFQPEG	800
VQFYNGKNGEL	VTYDIKTLQQ	INPP	(SEQ ID NO : 83)		824

FIGURE 48

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